

Basis *of* **Clinical** **Physiology**

Vol. 1

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Prof. Dr. Muhammad Akram

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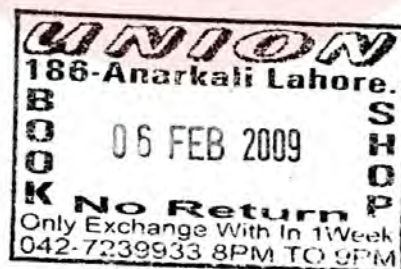
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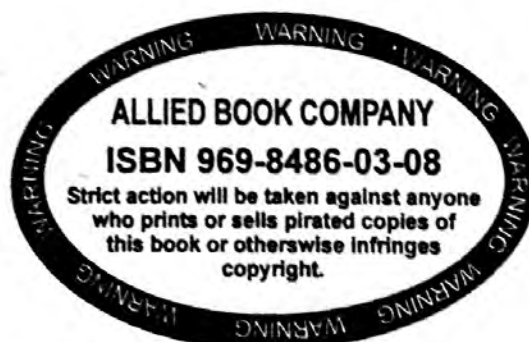
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DEDICATED TO

“LATE PROF. DR. MUHAMMAD NAWAZ SAHIB”

EX-PRINCIPAL AND PROFESSOR OF PHYSIOLOGY,

RAWALPINDI MEDICAL COLLEGE, RAWALPINDI.

DEVOTED AND MASTER TEACHER AND SPECIALIST IN CNS PHYSIOLOGY,

THE MENTOR, GROOMER AND WHO INSPIRED THE AUTHOR TO WRITE

THIS BOOK AND BECAME DEAR TO HIS CREATOR UNBLEMISHED,

LEAVING BEHIND AN EXAMPLE OF SINCERITY, DEVOTION AND

DEDICATION.

اللَّهُمَّ اغْفِرْ لَهُ وَارْحَمْهُ

Preface

In such modern days and rapidly advancing scientific world, it becomes more and more difficult for the medical students to identify, understand and let alone (leaving to themselves) to remember the essentials of medical lore. The established physicians have problems too, for it is not easy for them to keep abreast of the changes taking place in the diverse areas of medical practice; which are becoming increasingly the domains of super specialists.

The purpose of this book is to help medical students both undergraduates (M.B.B.S., B.D.S., B.Sc. Physiotherapy) and postgraduates (M.Phil, FCPS, Diplomas in Medicine and D.Pharmacy) to master the essential core of knowledge, develop the ability to correlate the basic facts with the clinical features, and to facilitate the understanding of the disease mechanism i.e. pathophysiology.

The "Basis of Clinical Physiology" Volume-I (Chapters 1-10) presents essentials of cardiovascular physiology, electrocardiography (ECG), fluid-electrolyte balance, renal physiology, space physiology, gastroenterology and functional assessment of vital organs of the body in particular; and cellular physiology, neuromuscular physiology, autonomic nervous system and basic physiological processes in general.

The text has been divided into small paragraphs and important facts have been italicized to enhance the retention power. In fact, these paragraphs provide the core knowledge of "one best response" MCQs. The reader can even structure and administer MCQs. Each chapter is preceded by intriguing introduction in common man's language to provide an overview in a solitary glance.

The chapters included in Volume-I are according to the syllabus prescribed by the Higher Education Commission (HEC) and the University of Health Sciences (UHS).

Acknowledgements

The impetus and advice to write this book is credited to Prof. Dr. Muhammad Nawaz who selected the author for specialization in Physiology in 1975 while working as medical officer in the Central Govt Hospital (CGH), Rawalpindi. Prof. Muhammad Nawaz trained the author in teaching, in acquiring post-graduation, in conducting examinations fairly under all kinds of pressures, and working honestly in odd circumstances. Once he remarked, "If you are just and impartial, fair and sympathetic to all irrespective of cast and creed, you will remain in the Beneficence and Protection of Allah Al-Mighty". Yet at another occasion, he reminded that no one on the face of earth is your opponent; otherwise you will not be able to love and respect the mankind.

His sense of dedication and patronisation was in fact due to "Fear of Allah" in his heart and high degree of sincerity towards all and sundry in the basic medical sciences in particular; and towards the human beings in general. He always worked for the pleasure of Allah; May Allah be pleased with him and shower His Mercies and Blessings forever in the eternal life.

The untiring and sustained efforts of Dr Muhammad Shafiq, senior demonstrator, requires full marks for his careful and cautioned approach towards precision and accuracy in the preparation of this manuscript. Moreover, I found Dr Muhammad Shafiq a perfect and sincere counsellor during the publication of this book.

My family, especially my wife endured with patience all irregularities in the domestic affairs, because all the rooms were flooded with papers, pencils, proofs, books, atlases and transparencies. My family's movement in summer vacations, spring and winter holidays all remained in inertia. Actually, the whole family contributed towards completion of this book. My son, Engr. Muhammad Abdullah helped simplifying the physical laws, equations and explaining symbols and units in the bio-physical aspects in the book, particularly in chapters on "*cardio-vascular and respiratory physiology*". He also provided extremely useful technical and computer assistance for which I am extremely grateful to him.

I am thankful to Mr. Muhammad Javed Iqbal for his speedy computer typing, Mr. Sharaz Ahamd Saddiqui started preparing this manuscript and designed the title

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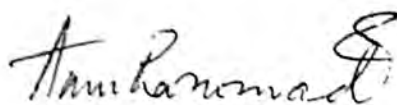
Mr. Muhammad Jameel, Managing Director of Sunflower Printers has won the author's confidence and kept the confidentiality of the manuscript / book and provided whole time printing facilities in a very cordial and homely environment.

M/s. Allied Book Company provided full cooperation in supplying the latest information, data and books. In addition they furnished the author with recent and advanced trends in printing of the text book. I am pleased to recommend Allied Book Company as sole stockist and distributor as they are expert and sincere in country wide distribution of books of Pakistani authors.

The dream of writing a text book came true by the Grace of All Mighty Allah, Most Gracious, Most Merciful.

“الْحَمْدُ لِلَّهِ رَبِّ الْعَالَمِينَ”

“Praise be to Allah The Cherisher and Sustainer of the Worlds”



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&
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This Book belongs to
Aamir Ali Bilal

PHYSIOLOGY THE QUEEN OF MEDICINE

INTRODUCTION:

Physiology is the study of how the living body works. Physiology embraces all levels of body functions, from molecules to populations. The study includes the power-giving mitochondria, the protein-making ribosomes, thinking brain and the beating heart.

Physiology is as broad as life. The nerve cells of squids and the kidneys of salamanders, for example, work almost like their counterparts in humans. Physiologists learn by observation, hypothesis, and experiment; the same commonsense methods used by all scientists. Physiologists may observe, for example, that the skin reddens upon exposure of the body to heat. If the experiment verifies the hypothesis, they publish the results and proceed to other experiments. Sometimes, an ugly fact destroys the beautiful hypothesis, in such a situation they make another hypothesis and try again.

Physiologists are helped by intuition and serendipity. Intuition is revelation without reasoning. Such revelations come suddenly, sometimes in the office or laboratory, sometimes at home or in the playground. Serendipity is an unexpected finding of something valuable. One of the physiologists while attempting to insert stimulating electrodes into the rear of a rat's brain, put them too far forward. By doing so, he discovered the pleasure system. Unexpected findings are common in physiology, but they benefit only those who understand them.

Physiologists, by and large, study normal functions, but they readily accept evidence from disease. Diseases are the experiments of nature. Disease states can be viewed as physiology gone wrong, or patho-physiology; and for this reason an understanding of physiology is absolutely essential for the study and practice of medicine. Indeed many

physiologists are actively engaged in research on the physiological bases of a wide range of diseases. From insulin-deficient diabetics, for example, physiologists learn about functions of the pancreas. Our bodies perform automatically, for the most part, and in ways that preserve life i.e. "the right response for almost any provocation".

DEFINING PHYSIOLOGY?

It is a study of *dynamic inter-relationships* that exists among cells, tissues and organs. In humans, the specialized cell groups include a gastro-intestinal system to digest and absorb food, a respiratory system to take up oxygen (O_2) and eliminate carbon dioxide (CO_2), cardio-vascular system to distribute O_2 , reproductive system to perpetuate the species, nervous and endocrine systems to co-ordinate and integrate the functions of other systems.

The typical cells combine to form tissues, different tissues compose organs and different organs constitute a system.

All human cells originate from a single fertilized cell. During development, cell division and specialization give rise to trillions of cells with a wide variety of cell types such as nerve, muscle, bone, fat and blood cells. Each cell type has important characteristics, which are critical to normal function of the body as a whole. Cells of each tissue possess tissue specific properties e.g., muscle cells contract, nerve cells conduct impulses; and endocrine cells secrete hormones. The four basic cell types are epithelial, connective-tissue cells, muscle and nerve cells.

EPITHELIAL CELLS:

Epithelial cells are specialized for the selective secretion and absorption of ions and organic molecules. They are located mainly at the surfaces

that either cover the body or individual organs or line the walls of various tubular and hollow structures within the body. Epithelial cells, which rest on a homogeneous non-cellular material called the basement membrane, form the boundaries between compartments and function as selective barriers regulating the exchange of molecules across them. For example, the epithelial cells at the surface of the skin form a barrier that prevents most substances in the external environment from entering the body through the skin. Epithelial cells are also found in glands that form from the invagination of epithelial surfaces.

CONNECTIVE-TISSUE CELLS:

Connective-tissue cells, as their name implies, have the major function of connecting, anchoring, and supporting the structures of the body. Many connective-tissue cells secrete into the fluid surrounding them, molecules that form a matrix consisting of various types of protein fibres embedded in a ground substance made of complex sugars, proteins, and crystallized minerals.

MUSCLE CELLS:

Muscle cells are specialized to generate the mechanical forces that produce force and movement. They may be attached to bones and produce movements of the limbs or trunk. They may be attached to skin, as for example, the muscles producing facial expressions, or they may enclose hollow cavities so that their contraction expels the contents of the cavity, as in the case of the pumping action of the heart.

NERVE CELLS:

Nerve cells are specialized to initiate and conduct electric signals, often over long distances. A signal may influence the initiation of new electric signals in other nerve cells, or it may influence secretion by a gland cell or contraction of a muscle cell. Thus, nerve cells provide a major means of controlling the activities of other cells. Their activity also underlines such phenomena as consciousness, perception, and cognition.

BODY REGIONS AND SPATIAL PLANES:

Human body can be divided into four major regions. Each region is further divided into sub-divisions (fig. 1.1).

1. Head: a) Cranial region.
b) Facial region.
2. Neck: Cervical region
3. Trunk: a) Thoracic region.
b) Abdominal region.

- c) Pelvic region.
4. Limbs: a) Upper limbs.
b) Lower limbs.

SPATIAL PLANES OF HUMAN BODY:

To understand various physiological phenomena it is quite imperative to be familiar with spatial planes of the human body e.g., ECG leads are described in the frontal and horizontal planes. Just as there are three planes in space (i.e., three dimensions), the body has three spatial planes:

1. Frontal or coronal plane.
2. Mid-sagittal or median sagittal plane.
3. Transverse or horizontal plane.

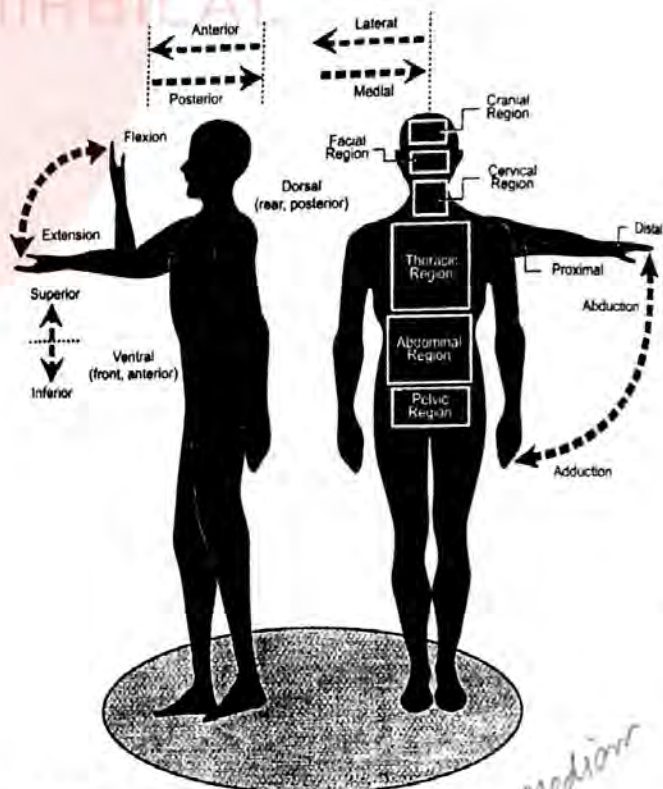


Fig. 1.1: Body planes and regions.

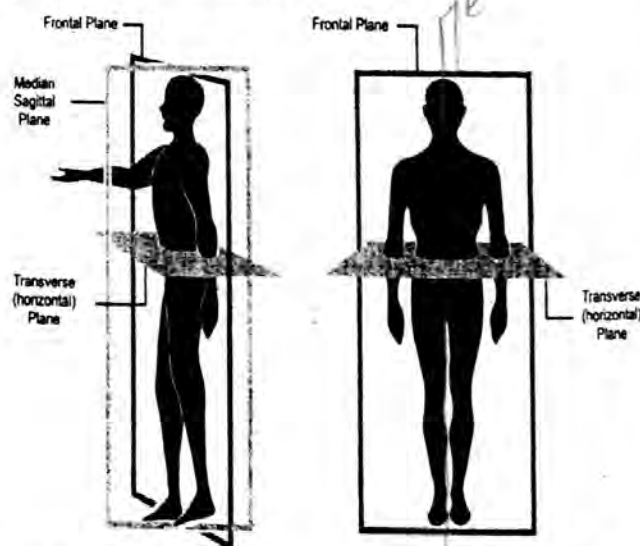


Fig. 1.2: Spatial planes: frontal, median sagittal and transverse.

The frontal plane passes vertically through the body, dividing the body into anterior or ventral and posterior or dorsal halves (fig. 1.2)

The median sagittal plane also passes vertically through the body, but this plane divides into right and left halves.

The transverse plane passes horizontally through the body from front to rear and divides the body into upper and lower halves.

EXTERNAL ENVIRONMENT:

External environment always keeps on changing. Man is a tough, ubiquitous and global animal. He can be found in the Polar regions of this small limited world, or in the higher ranges of Andes or in huge towns in the humid heat on the seacoast. He is capable of exploring the outer space. Man is engaged in constant struggle against viruses, bacteria, protozoa and worms. Many species become his parasite. Doctor is particularly concerned with the responses to parasites, bacteria, social mal-adjustments and violence.

INTERNAL ENVIRONMENT:

The blood and lymph, which bathe the cells of the human body, are conceived as an internal environment, which protect the cells of the organs of the body from variations occurring in the external environment. Canon in 1929 introduced the term homeostasis to describe this principle.

BODY FLUID COMPARTMENTS:

The fluid in the body is enclosed in "compartments." The volumes of the body-fluid compartments are conventionally measured in terms of water, since water is by far the major component of the fluids in each compartment.

Compartmentalization is an important general principle in physiology. Epithelial barriers form the compartments. The properties of the barriers determine the movements of substances between adjacent compartments. These movements in turn account for the differences in the composition of the fluids in different compartments.

The intracellular fluid (ICF) is separated from the extra-cellular fluid (ECF) by molecular membranes that surround the cells. In contrast, the two components of extra-cellular fluid i.e. the interstitial fluid (ISF) and the blood plasma are separated by the cellular wall of the smallest blood vessels, the capillaries. This barrier normally keeps 80 percent of the extra-cellular fluid in the interstitial fluid compartment and restricts proteins mainly to the plasma.

The cells that make up the human body exist in an internal sea of ECF. From this fluid the cells take up oxygen and nutrients and discharge waste products into it. The ECF is more dilute than the water of present-day sea/ocean.

The ECF is divided into two components:

1. Interstitial fluid (ISF).
2. Circulating blood plasma.

The plasma and formed elements of blood i.e. red blood cells (RBC), white blood cells (WBC), and platelets fill the vascular system and constitute the total *blood volume*. The ISF is that part of the ECF which is outside the vascular system, bathing the cells. About one third of the total body water (TBW) is ECF and remaining two third is the intra-cellular fluid (ICF). Trans-cellular fluid (TCF) which is 2% of the ECF keeps on circulating as special body fluid in the form of cerebro-spinal fluid, aqueous humour and in the contents of GIT secretions.

ORGANISATION OF THE BODY:

In an average young adult male, 18% of body weight is protein and related substances, 7% are minerals, and 15% is fat. The remaining 60% is water.

HOMEOSTASIS:

Homeo in Greek means the like or same. Homeostatic processes are those physiological processes/ reactions that tend to restore the internal environment to a steady or resting state.

Examples:

1. Heavy physical exercise raises the temperature of blood and acidity.
2. A meal raises the level of blood sugar, and drinking water lowers the osmolarity of the blood. Exercise, food and water, each initiate responses, which cause the blood to return to normal state.

EXERCISE AND BODY TEMPERATURE:

Normal temperature of blood is 37 – 38°C. Running for 20 minutes produces 200 Kcal of heat. This heat can raise the body temperature (of 65 Kg man) by 39.6 – 40.6°C. While running, one starts to perspire and may lose 200 ml of sweat. The sweating reduces the rise in body temperature and temperature returns to normal soon after the end of exercise.

EXERCISE AND ACIDITY OF BLOOD (pH):

The blood is normally alkaline. The hydrogen ion concentration is about 40 ng (1 nanogram = 10^{-9} g) corresponding to a pH value of 7.4. During exercise the muscles produce carbon dioxide, which is an acid in solution. However, the acidity of blood rises only very slightly during exercise and pH seldom

falls by more than 0.05. This is partly due to buffering power of blood, but exercise increases the rate of breathing so that CO_2 is blown off almost as rapidly as it is formed.

FASTING AND BLOOD GLUCOSE:

The blood of a fasting man contains 60 – 90 mg of glucose per 100 ml of blood. The tissues utilize it continuously and the level is normally maintained by absorption of dietary intake of carbohydrates. After a meal blood sugar may rise to 140 – 160 mg per 100 ml of blood. This excess is stored in the liver and muscles. Yet a man may fast for 2 – 3 weeks and his blood sugar is well maintained. The level in the blood is kept constant (glucose homeostasis) by the formation of glucose from proteins and glycerol.

BASIC PHYSIOLOGICAL PROCESSES

DIFFUSION:

It is a process by which a gas or substance in solution expands, because of the motion of its particles to fill all of the available volume.

The particles of a substance dissolved in a solvent are in continuous random motion. In regions where they are abundant, they frequently collide. They, therefore, tend to spread from regions of higher concentration to regions of low concentration, until the concentration becomes uniform throughout the solution.

MAGNITUDE:

The magnitude of the diffusing tendency is proportionate to the difference in concentration.

ELECTRICAL POTENTIAL:

Diffusion of ions is also affected by their electrical charge. Whenever there is a difference in potential between two regions, *positively* charged ions move along this electrical gradient to the more *negatively* charged region. Negatively charged ions move in the opposite direction.

Diffusion through a membrane:

Diffusion through the cell membrane depends upon the *permeability coefficient*, which is defined as the *facility with which a solute can diffuse through a cell membrane*; which depends upon (1) nature of solute and (2) nature of cell membrane.

RATE OF DIFFUSION:

Depends upon following factor:

1. SOLUBILITY:

The lipid soluble substances can cross (diffuse) the membrane with facility and ease.

2. HYDROPHILICITY:

The greater the number of (OH^-) hydroxyl groups on an organic molecule, the greater is the hydrophilicity. The permeability of cell membrane to a substance is inversely related to the hydrophilic nature of the substance i.e. greater the hydrophilicity slower will be the diffusion rate e.g. hydrophilic substances such as Na^+ , K^+ , sugars and amino acids will penetrate the cell membrane only very slowly. The permeability constant of Na^+ is one hundred millionth that of water.

3. ELECTRICAL CHARGE:

It is generally true that the electrically charged particles penetrate cell membrane very slowly. **ANIONS** i.e. OH^- , Cl^- and HCO_3^- have very high permeability as compared to the **CATIONS** i.e. Na^+ and K^+ . Generally speaking cell wall favours the diffusion of anions over cations (except H^+).

4. MOLECULAR SIZE:

Greater the molecular weight, the smaller the permeability co-efficient i.e. larger the particle slower the thermal motion, and consequently smaller is the rate of diffusion.

5. POLAR MOLECULES:

The permeability co-efficient of polar molecules (charged molecules) such as proteins, nucleic acids and viruses is exceedingly small. All such molecules are transported by special mechanisms.

FACILITATED DIFFUSION:

Facilitated diffusion is a passive form of transport across a membrane with the help of a carrier molecule.

Many ions, urea, glucose, fructose, galactose, and certain vitamins, which are lipid-insoluble, diffuse through the phospholipid bilayer, can cross the plasma membrane by facilitated diffusion. In this process, the substance moves down its concentration gradient from a region of higher concentration to a region of lower concentration with the help of specific integral proteins in the membrane that serve as water-filled channels or transporters (carriers) for each type of substance. It is a passive transport process that doesn't consume ATP. The rate of facilitated diffusion is determined by the size of the concentration difference on the two sides of the membrane and the number of channels or transporters available.

At the level of the organism, facilitated diffusion may resemble the transport of oxygen from the lungs to the tissues. The carrier is the haemoglobin, the substance to be carried is the oxygen. The carrier demonstrates *specificity* i.e. it combines with oxygen but not with nitrogen; *saturation* i.e. an

increase in alveolar oxygen tension beyond certain level doesn't yield a proportionate increase in oxygen transport, **competition**, carbon monoxide competes with oxygen and prevents oxygen uptake.

Glucose is an important substance that enters many body cells by facilitated diffusion, as follows:

1. First, glucose attaches to a transporter on the outside of the membrane. Different cells have different glucose transporters, which are called GLUT_1 , GLUT_2 , and so on numbered in the order they were discovered.

2. Then the transporter changes shape.

3. Glucose passes through the membrane and is released inside the cell.

After glucose has entered the cell by facilitated diffusion, an enzyme called a kinase attaches a phosphate group to produce glucose 6-phosphate. This reaction keeps the intracellular concentration of glucose itself very low so that the concentration gradient always favours facilitated diffusion of glucose into, and not out of cells.

Selective permeability of the plasma membrane is often regulated to achieve homeostasis. For example, facilitated diffusion of glucose into certain cells (those having GLUT_4) is greatly accelerated by the hormone insulin. Thus insulin lowers blood glucose level by speeding the movement of glucose from the blood into body cells.

TRANSPORT:

Vital substances like sugars and amino acids cross the cell membrane at very low rates. At many locations substances have to be transported against a concentration gradient or against an electrical gradient. Passive transport processes cannot achieve this; it requires active and special modes of transport mechanisms, which accelerate the rate of transport.

ACTIVE TRANSPORT:

Active transport occurs against a concentration gradient or against an electrical gradient.

It is a process in which molecular movement across the membrane occurs with a carrier protein; and which requires a *coupled input of metabolic energy*. Thus an active transport process is defined, not by demonstrating that the flux is *thermo-dynamically uphill*, but only by demonstrating that the flux is *coupled to metabolism i.e. energy (ATP) dependent*.

ACTIVE UPHILL TRANSPORT:

The substances are transported uphill across membranes from regions of low to regions of high electro-chemical potential. In this mechanism

metabolic process provides energy for the transport process.

The energy required for active transport is derived from the hydrolysis of substances such as ATP. If there is no coupling with metabolic process, transport is passive. The $\text{Na}^+ - \text{K}^+$ ATPase in the cell membranes, the sarcoplasmic Ca^{++} ATPase in the muscle, and the H^+ -ATPase in the renal tubules of the kidney are examples of such pumps, which transport Na^+ , K^+ , Ca^{++} and H^+ respectively (fig 1.3).

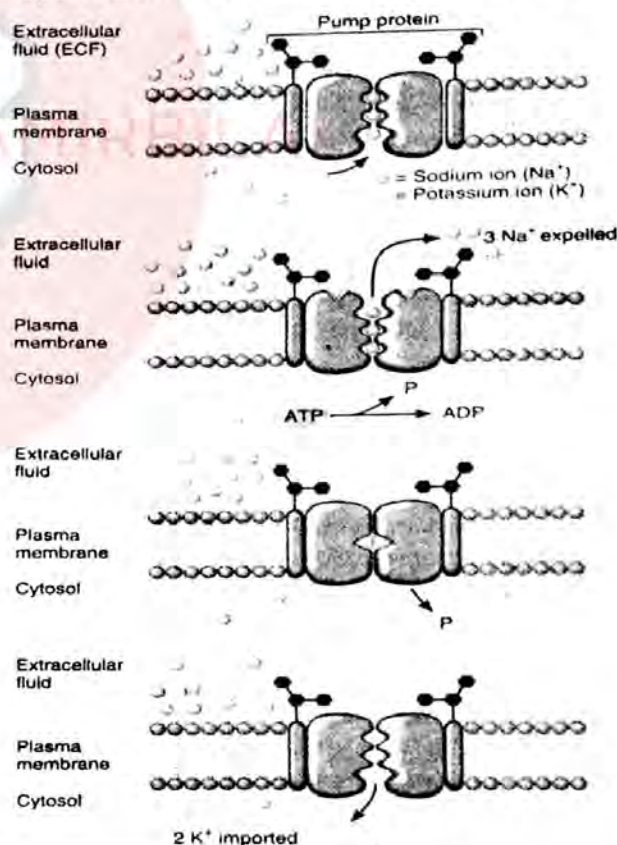


Fig. 1.3: Active transport: $\text{Na}^+ - \text{K}^+$ ATPase pump.

ACTIVE DOWNHILL TRANSPORT:

A transport process in which net flow of substance is from a region of high to a region of low electro-chemical potential, which is not necessarily spontaneous, rather a metabolic energy source is coupled to such a downhill process; so as to *increase net rate of flow* of the substance.

Active transport is carrier-mediated and metabolic energy is required. If energy supply is blocked, active transport ceases e.g. human erythrocyte (RBC) has higher K^+ in normal conditions than in the serum. When RBCs are refrigerated then active transport ceases, and K^+ slowly leak out of the cells, until intracellular and extra-cellular K^+ concentrations are equal. When the blood temperature is restored to 37°C , provided there is an energy source such as glucose in the serum active transport resumes and intracellular K^+ increases towards normal level.

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It is a process in which molecular movement across the membrane occurs with a carrier protein; and which requires a coupled input of metabolic energy. Thus an active transport process is defined, not by demonstrating that the flux is thermo-dynamically uphill, but only by demonstrating that the flux is coupled to metabolism i.e. energy (ATP) dependent.

ACTIVE UPHILL TRANSPORT:

The substances are transported uphill across membranes from regions of low to regions of high electro-chemical potential. In this mechanism

metabolic process provides energy for the transport process.

The energy required for active transport is derived from the hydrolysis of substances such as ATP. If there is no coupling with metabolic process, transport is passive. The $\text{Na}^+ - \text{K}^+$ ATPase in the cell membranes, the sarcoplasmic Ca^{++} ATPase in the muscle, and the H^+ -ATPase in the renal tubules of the kidney are examples of such pumps, which transport Na^+ , K^+ , Ca^{++} and H^+ respectively (fig 1.3).

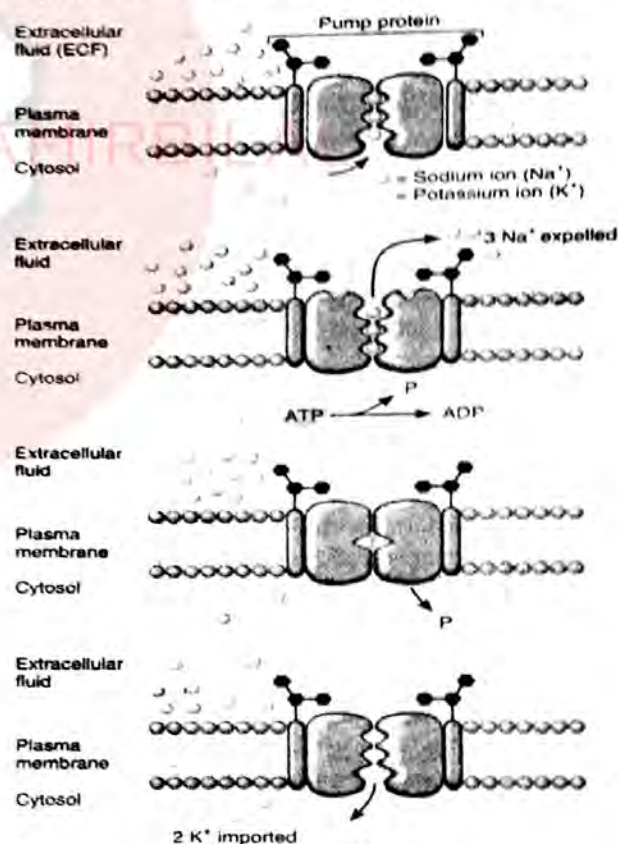


Fig. 1.3: Active transport: $\text{Na}^+ - \text{K}^+$ ATPase pump.

ACTIVE DOWNHILL TRANSPORT:

A transport process in which net flow of substance is from a region of high to a region of low electro-chemical potential, which is not necessarily spontaneous, rather a metabolic energy source is coupled to such a downhill process; so as to increase net rate of flow of the substance.

Active transport is carrier-mediated and metabolic energy is required. If energy supply is blocked, active transport ceases e.g. human erythrocyte (RBC) has higher K^+ in normal conditions than in the serum. When RBCs are refrigerated then active transport ceases, and K^+ slowly leak out of the cells, until intracellular and extra-cellular K^+ concentrations are equal. When the blood temperature is restored to 37°C , provided there is an energy source such as glucose in the serum active transport resumes and intracellular K^+ increases towards normal level.

The substance to be transported combines with specific membrane bound carrier molecules and crosses the cell membrane as a part of substrate-carrier molecule complex. The carrier molecules are:

1. Confined to the cell membrane, and shuttle back and forth from one side of the membrane to the other.
2. The carrier works like a ferryboat that remains in the sea and transports materials from one side of the beach to the other side.
3. Carrier accelerates the transport across the membrane.
4. Carrier reduces the thermal energy needed by the substrate molecule to leave the aqueous phase and to enter the membrane phase.

STEPS OF CARRIER MEDIATED TRANSPORT:

The carrier molecules are confined to the membrane region. The substances are transported across the cell membrane according to the following sequence:-

1. Substance combines with the carrier (fig. 1.4).
2. Substance-carrier complex passes to cytoplasmic side.
3. Substance-carrier complex dissociates and the substance is discharged into the cytoplasm.
4. Carrier is enzymatically degraded into an inactive form, i.e. a form that exhibits low affinity for the substance.
5. Inactive carrier passes to extra-cellular side of the cell membrane (fig. 1.4).

CHARACTERISTICS OF CARRIER MEDIATED TRANSPORT:

1. SATURATION:

When there is no carrier, the rate of transport is proportional to the concentration difference. If this difference doubles, the rate of transport doubles. In carrier mediated transport, when all the carrier molecules are in constant use, then further increase in concentration will not appreciably increase the rate of transport, because the carrier system is saturated and un-occupied carriers are not available e.g. an increase in alveolar oxygen tension beyond certain levels do not yield a proportionate increase in oxygen transport. Similarly, in diabetes mellitus, when plasma glucose level is elevated and tubular maximum for glucose re-absorption is exceeded, appreciable amount of glucose appears in the urine. This is because carrier system is saturated, and "transport maximum" is reached, called as *transport maxima of glucose (TmG)*. In some individuals, the glucose transport mechanism in the renal tubules is congenitally defective; so that glucosuria is present

at normal plasma glucose levels. This condition is called as *renal glucosuria*.

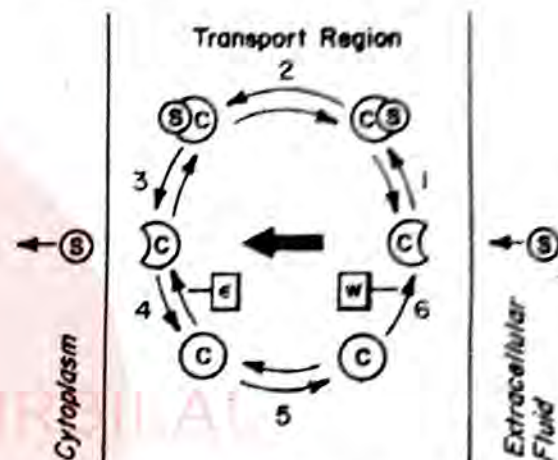


Fig. 1.4: Model for active transport. The carrier molecules (large circles) are confined to the membrane region. There is a net transport of substance (small circles) from the extra cellular fluid to the cytoplasm.

2. COMPETITIVE INHIBITION:

Two substances, which attach to the same carrier compete for the carrier system e.g. carbon monoxide (CO) competes with oxygen for the same carrier (Hb) and prevents oxygen uptake.

3. SPECIFICITY:

One carrier molecule may transport one amino acid or group of amino-acid while other transports one sugar or group of sugars. The specificity is never perfect and a given carrier may carry a number of substances of related chemical structure, e.g. D-glucose system also transports other sugars. These include D-mannose, D-galactose and D-xylose etc.

PRIMARY ACTIVE TRANSPORT (THE SODIUM PUMP):

Movement of a substance against the concentration gradient by the direct utilization of energy is called as primary active transport. The most prevalent primary active transport mechanism expels sodium ions (Na^+) from cells and brings potassium ions (K^+) into the cell. These pumps maintain a low concentration of Na^+ in the cytosol by pumping it out against the concentration gradient. They also move K^+ into cells against its concentration gradient.

Because of the ions it moves, this primary active transport mechanism is called the Na^+-K^+ pump or, more simply, the sodium pump. All cells have hundreds of sodium pumps in each square micrometer (μm^2) of membrane surface. Since the pump is a protein that acts as an enzyme to split the needed ATP, it is also called Na^+-K^+ ATPase.

The sodium pump, which is actually a group of similar pumps with slightly different properties may operate as diagrammed in expelling three Na^+ each time they import two K^+ . Others exchange one Na^+ for each K^+ . The sodium pump must work continuously because K^+ and Na^+ slowly leak across the plasma membrane through leakage channels.

SECONDARY ACTIVE TRANSPORT (SYM-PORTERS AND ANTI-PORTERS):

The sodium pump maintains a large concentration difference of Na^+ across the plasma membrane. Normally, the plasma membrane is fairly impermeable to Na^+ because there are few leakage channels. Secondary active transport proteins harness the energy in the Na^+ concentration difference by providing easy routes for Na^+ to leak into the cells. This is like allowing water behind a dam to flow through an outlet pipe and turn a turbine to produce electrical power. This potential energy of sodium ions concentration gradient is then utilized for the transport of other substances like glucose, amino acids etc.

When two substances move in the same direction across the plasma membrane, the process is called symport or co-transport (fig.1.5). For example, glucose, galactose, and amino acids enter cells lining the small intestine and the kidney tubules via Na^+ symports. This is how dietary monosaccharides and amino acids are absorbed and nutrients filtered by the kidneys are returned to the blood stream so that they are not lost in the urine.

Through antiporter or counter transport two substances move in opposite directions across the plasma membrane. In most cells, Na^+ - Ca^{++} antiporters keep Ca^{++} concentration low in the cytosol.

Likewise, Na^+ - H^+ anti-porters help to regulate the cytosol's pH (H^+ concentration) by using the Na^+ gradient to expel H^+ .

The protein that forms a symporter or anti-porter works by simultaneously binding to Na^+ and another substance; and then changing its shape so that both substances cross the membrane at the same time. *The larger the concentration difference of Na^+ across the membrane, the faster the secondary active transport.*

ENDOCYTOSIS (BULK TRANSPORT):

Endocytosis is a process when bulk material solid or liquid (pinocytosis) is captured by the cell, by throwing out a curtain of cell membrane that encloses it; and the captured mass is taken into the cell in a membrane-enclosed vesicle.

Bulk transport means that large number of particles, droplets of fat or numerous molecules pass at once through the membrane.

Processes that bring large quantities of matter into the cell are called endocytosis, and those that release material from the cell are called exocytosis.

There are three forms of endocytosis:

1. PHAGOCYTOSIS

Phagocytosis, or "cell eating", is the process of engulfing particles such as bacteria, dust, and cellular debris. Neutrophils (a class of white blood cells), for example, protect the body from infection by phagocytizing (engulfing) and killing bacteria. A neutrophil spends most of its life crawling about in the connective tissues by means of blunt foot-like extensions called pseudopodia. When a neutrophil encounters a bacterium, it surrounds it with its pseudopodia and traps it in a phagosome (vacuole) i.e. "bubble" in the cytoplasm surrounded by a unit

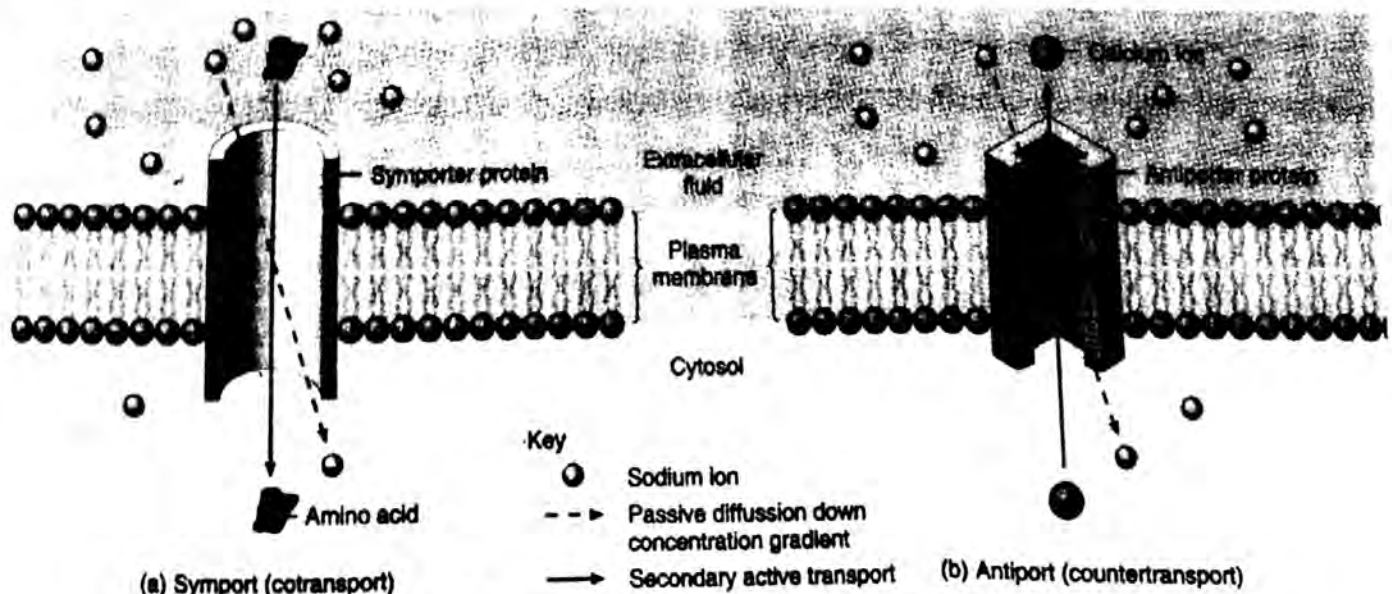


Fig. 1.5: Secondary active transport (a) symport, (b) antiport.

membrane. A lysosome subsequently merges with the vacuole, converting it to a phagolysosome, and contributes enzymes that destroy the invader. In general, phagocytosis is a way of keeping the tissues free of debris and infectious microorganisms. Some cells called macrophages (literally means "big eaters") take up the equivalent of 25% of their own volume per hour.

2. FLUID-PHASE PINOCYTOSIS:

Fluid-phase pinocytosis, or "cell drinking", is the process of taking in droplets of extra-cellular fluid (ECF) containing molecules of some use to the cell. While phagocytosis occurs in only a few specialized cells, pinocytosis occurs in all human cells. The process begins as the plasma membrane becomes dimpled, or caved in, at points. These pits soon separate from the surface membrane and form small membrane-bound pinocytotic vesicles in the cytoplasm. The vesicles contain droplets of the ECF with whatever molecules happened to be there.

3. RECEPTOR MEDIATED ENDOCYTOSIS:

Receptor-mediated endocytosis is more selective. It enables a cell to take in specific molecules from the ECF with a minimum of unnecessary fluid. Molecules in the ECF bind to specific receptors on the plasma membrane and sink in at this point, creating a pit coated with a peripheral membrane protein called clathrin. The pit soon pinches off to form a clathrin-coated vesicle in the cytoplasm. Clathrin may serve as an "address label" on the coated vesicle that directs it to an appropriate destination in the cell, or it may inform other structures in the cell what to do with the vesicle.

One example of receptor-mediated endocytosis is the uptake of low-density lipoproteins (LDL) i.e. protein-coated droplets of cholesterol and other lipids in the blood. The thin endothelial cells that line our blood vessels have LDL receptors on their surfaces and absorb LDL in clathrin-coated vesicles. Inside that cell, the LDL is freed from the vesicle and metabolised, and the membrane with its receptors is recycled to the cell surfaces. Most of what we know about receptor-mediated endocytosis comes from studies of a hereditary disease called familial hypercholesterolaemia, which dramatically illustrates the significance of this process to the cardiovascular health.

Endothelial cells also imbibe insulin by receptor-mediated endocytosis. Insulin is too large a molecule to pass through channels in the plasma membrane, yet it must somehow get out of the blood and reach the surrounding cells if it is to have any effect. Endothelial cells take up insulin by receptor-mediated endocytosis, transport the vesicles across

the cell, and release the insulin on the other side, where tissue cells await it. Such transport of a substance across a cell is called transcytosis.

Receptor mediated endocytosis is not always to our benefit; hepatitis, poliomyelitis, and AIDS viruses "trick" our cells, taking them in by receptor mediated endocytosis.

EXOCYTOSIS:

Exocytosis occurs, for example, when endothelial cells release insulin to the tissue fluid, breast cells secrete milk, gland cells release hormones, and sperm cells release enzymes for penetrating an egg. It bears a superficial resemblance to endocytosis in reverse. A secretory vesicle in the cell migrates to the surface and "docks" on peripheral proteins of the plasma membrane. These proteins pull the membrane inward and create a dimple that eventually fuses with the vesicle and allows it to release its contents.

Question arises if endocytosis continuously takes away bits of plasma membrane to form intracellular vesicles and vacuoles, why does not the membrane grow smaller and smaller? Another purpose of exocytosis, however, is to replace plasma membrane that has been removed by endocytosis or become damaged or worn out. Plasma membrane is continuously recycled from the cell surface into the cytoplasm and back to the surface.

FAMILIAL HYPERCHOLESTEROLAEMIA:

A hereditary disease called familial hypercholesterolaemia dramatically illustrates the significance of LDL receptors and receptor-mediated endocytosis. Persons with this disease have an abnormally low number of LDL receptors. Their cells therefore absorb less cholesterol than normal, and the cholesterol remains in the blood. Their blood cholesterol levels may be as high as 1,200 mg/dl compared to a normal level of about 200 mg/dl. People who inherit the gene from both parents typically have heart attacks before the age of 20 (sometimes even in infancy) and seldom survive beyond the age of 30.

OSMOSIS:

It is the diffusion of water across selectively permeable membrane, such as plasma membrane. A selectively permeable membrane is a membrane that allows water but not the solutes dissolved in water to diffuse through the membrane. Water diffuses from a solution with more water concentration into a solution with proportionately less water. The concentrations of solution are described in terms of solute concentration and not in terms of water concentration. Water diffuses from

less concentrated solution (less solute and more water) into the more concentrated solution (more solutes less water). Osmosis is important to cells because large volume changes caused by water movement disrupt normal cell function.

OSMOTIC PRESSURE:

It is the force required to prevent the movement of water by osmosis across a selectively permeable membrane.

DETERMINATION OF OSMOTIC PRESSURE:

The osmotic pressure of a solution can be determined by placing the solution in a tube that is closed at one end by a selectively permeable membrane. The tube is then immersed in distilled water. Water molecules move by osmosis through the membrane into the tube, forcing the solution to move up in the tube. As the solution rises into the tube, its weight produces hydrostatic pressure that moves water out of the tube into the distilled water surrounding the tube. At equilibrium, net movement of water stops, which means that the movement of water into the tube by osmosis is equal to the movement of water out of the tube caused by hydrostatic pressure. The osmotic pressure of the solution in the tube is equal to the hydrostatic pressure that prevents net movement of water into the tube (fig. 1.6: a and b).

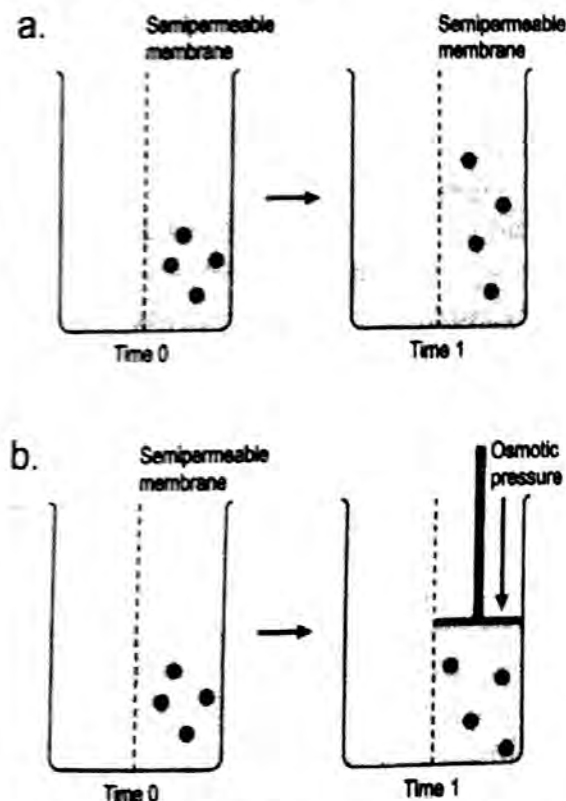


Fig. 1.6: a. Osmosis; water moves from low solute concentration to higher concentration. b. Osmotic pressure; the pressure required to stop the movement of water molecules into the solution is called osmotic pressure.

Thus, greater the concentration of a solution, greater the osmotic pressure of that solution, and greater the tendency for water to move into the solution. Three terms describe the osmotic pressure of the solutions; isosmotic, hyper osmotic, and hyposmotic.

ISOSMOTIC SOLUTION:

Solutions with same concentration of solute particles have same osmotic pressure, and it is called as isosmotic solution. The solutions are still isosmotic even if the types of solutes are different in the two solutions.

If one solution has a greater concentration of solutes and, therefore, a greater osmotic pressure than another solution, the first solution is called as hyperosmotic. The other more dilute solution is called as hyposmotic and has a lesser osmotic pressure.

ISOTONIC SOLUTION:

The term tonicity is used to describe the osmolarity of a solution relative to plasma. Solutions that have the same osmolarity as plasma are said to be isotonic; those with greater osmolarity are hypertonic; and those with lesser osmolarity are hypotonic. If a cell is placed into a solution in which it neither shrinks nor swells, the solution is said to be isotonic. If a cell is placed into a solution and water moves out of the cell by osmosis, causing the cell to shrink, the solution is called hypertonic. If a cell is placed into a solution and water moves into the cell by osmosis, causing the cell to swell, the solution is called hypotonic.

CRENATION AND LYSIS:

An isotonic solution may be isosmotic, because isosmotic solutions have the same concentration of solutes and water as the cytoplasm of the cell. There is no net movement of water and the cell neither swells nor shrinks. Hypertonic solutions can be hyperosmotic and have a greater concentration of solute molecules and a lower concentration of water than the cytoplasm of the cell. Therefore, water moves by osmosis from the cell into the hypertonic solution, causing the cell to shrink, a process called crenation. Hypotonic solutions can be hyposmotic and have a smaller concentration of solute molecules and a greater concentration of water than the cytoplasm of the cell. Therefore, water moves by osmosis into the cell, causing it to swell. If the cell swells enough, it can rupture, a process called lysis. Solutions injected into the circulatory system or the tissues must be isotonic because crenation or swelling of cells disrupts their normal function and can lead to cell death.

The term osmotic refers to the concentration of the solutions, and the term tonic refers to the tendency

of cells to swell or shrink. These terms should not be used interchangeably. Not all isosmotic solutions are isotonic. For example, it is possible to prepare a solution of glycerol and a solution of mannitol that are isosmotic to the cytoplasm of the cell. Because the solutions are isosmotic, they have the same concentration of solutes and water as the cytoplasm. Glycerol, however, can diffuse across the plasma membrane, and mannitol cannot. When glycerol diffuses into the cell, the solute concentration of the cytoplasm increases, and its water concentration decreases. Therefore, water moves by osmosis into the cell, causing it to swell, and the glycerol solution is both isosmotic and hypotonic. In contrast, mannitol cannot enter the cell, and the isosmotic mannitol solution is also isotonic.

FILTRATION:

Filtration is a form of transport taking place through a membrane permeable to water. If a pressure difference builds up between the two sides of the membrane, the fluid is pressed through it.

Filtration is a process in which particles are driven through a selectively permeable membrane by hydrostatic pressure gradient i.e. the force exerted on the membrane by water. A coffee filter provides an everyday example. The weight of the water on the filter is a force that drives water and dissolved matter through it, while the filter holds back larger particles (the coffee grounds).

In physiology, the most important instance of filtration is in the blood capillaries, where blood pressure forces fluid through gaps in the capillary wall. This is how, water, salts, nutrients, and other solutes are transferred from the blood stream to the tissue fluid and how the kidneys filter wastes from the blood. Capillaries hold back larger particles such as blood cells and proteins.

CONTROL SYSTEMS OF THE BODY:

Physiology is a study of the systems that control the processes of life. We prefer to live in our houses and the inside environment is kept at a comfortable temperature. In hot and humid weather we control the temperature by setting the thermostat of our split air-conditioner at an appropriate temperature like 26°C .

The control systems in the human body operate at different levels e.g. genetic control system at cellular level, organ control system at organ level (like vital organs regulate blood flow e.g. heart, brain and kidney) and whole body control systems like homeostatic control system.

1. CELLULAR CONTROL SYSTEM:

It operates in the cell to control intracellular functions

and life processes. The cell creates within its membrane-bound cytoplasm a micro-environment kept at a constant composition to allow the processes of the cell to proceed un-affected by the medium in which the cell is located.

2. ORGAN CONTROL SYSTEM:

The vital organs like brain, heart, kidney, skin and liver regulate their own blood flow. These organs have a dual control through metabolic and myogenic control mechanisms termed as auto-regulation.

3. HOMEOSTATIC CONTROL SYSTEM:

The internal environment of the body is kept in a steady state by coordination of various systems. Temperature homeostasis, for example, is maintained by autonomic and cardio-vascular systems.

Homeostasis denotes the relatively stable condition of the internal environment that results from the compensating regulatory responses performed by the homeostatic control system. Take the example of body temperature. Our subject is resting, in a room having a temperature of 20°C and moderate humidity. His internal body temperature is 37°C , and he is losing heat to the external environment because it is at a lower temperature. However, the chemical reactions occurring within the cells of his body are producing heat at a rate equal to the rate of heat loss. Under these conditions, the body undergoes no net gain or loss of heat and the body temperature remains constant.

WHAT IS STEADY STATE:

The steady state, defined as a system in which a particular variable (temperature, in this case) is not changing, but energy (in this case, heat) must be added continuously to maintain the "variable" constant. Steady states differ from equilibrium, in which a particular variable is not changing but no input of energy is required to maintain the constancy. The steady-state temperature in our example is known as the operating point (also termed the set point) of the thermo-regulatory system.

This example illustrates a crucial generalization about homeostasis: Stability of an internal environmental variable is achieved by the balance of inputs and outputs. In this case, the variable is body temperature that remains constant because metabolic heat production (input) equals heat loss from the body (output).

Now we lower the temperature of the room rapidly, say to 5°C , and keep it there. This immediately increases the loss of heat from our warm skin, upsetting the dynamic balance between heat gain

and loss. The body temperature therefore starts to fall rapidly, however, a variety of homeostatic responses occur to limit this fall:

1. The blood vessels to the skin are constricted, reducing the amount of warm blood flowing through the skin and thus reducing heat loss. At a room temperature of 5°C, however, blood vessel constriction is not able to eliminate completely the extra heat loss from the skin.

2. The subject curls up in order to reduce the surface area of skin available for heat loss. This helps a bit, but excessive heat loss still continues and body temperature keeps falling, although at a slower rate.

3. The person has a strong desire to put on more clothing, for "voluntary" behaviour responses are often crucial components in homeostasis, but no clothing is available. Clearly, then, if excessive heat loss (output) cannot be prevented, the only way of restoring the balance between heat input and output is to increase input, and this is precisely what occurs next.

4. He begins to shiver, and the chemical reactions responsible for the muscular contractions that constitute shivering produce large quantities of heat.

Indeed, heat production may transiently exceed heat loss so that body temperature begins to go back toward the value existing before the room temperature was lowered. It eventually stabilizes at a temperature, a bit below this original value. At this new steady state, heat input and heat output are again equal to each other. Here is another crucial generalization about homeostasis; stability of an internal environmental variable depends not upon the absolute magnitudes of opposing inputs and outputs, but only upon the balance between them. Homeostasis is also maintained through feedback control system. It has three types:

1. NEGATIVE FEED-BACK:

It is a process in which the body detects a change and activates mechanisms that negate or reverse it. When the negative feed back sets in, the response or output is "NEGATIVE" to the initiating stimulus.

Body temperature is also regulated by negative feed-back via "thermo-stat", a group of nerve cells in the base of brain (hypothalamus) that monitors the temperature of the blood. When the body temperature rises, the thermostat triggers heat losing mechanisms. One of these is vaso-dilation, the widening of blood vessels. When blood vessels of the skin dilate, warm blood flows closer to the body surface and radiates heat into the surrounding air. If this is not enough to return the body temperature to normal, sweating occurs; evaporation

of sweat from the skin has a powerful cooling effect. Conversely, if it is cold outside and the body temperature drops below 37°C, heat conserving mechanisms are initiated i.e. vaso-constriction, shivering and muscle tremors that generate heat. Thus heat loss is reduced by vaso-constriction and more heat is generated to restore body temperature to normal.

2. POSITIVE FEED-BACK:

It is a process in which a physiological change leads to enhance and amplify the change in the same direction and the response or output is positive to the initiating stimulus. An initial disturbance in a system sets off a train of events that increase the disturbance even further. Thus positive feedback does not favour stability and often abruptly displaces a system away from its steady-state operating point. Blood loss due to excessive bleeding leads to fall in blood pressure and vaso-dilation occurs instead of vaso-constriction, and a further fall in blood pressure culminates into irreversible shock, which often proves to be fatal.

Several important positive feed-back relationships occur in the body, which is beneficial e.g. blood clotting, protein digestion and generation of nerve impulse. The hormone oxytocin is released when the head of the baby presses against the cervix, and stimulates its nerve endings. Nerve signals travel to the brain, which in turn stimulate pituitary to secrete more oxytocin, setting the positive feed-back. The uterine contractions become more and more severe and intense and baby is delivered.

3. FEED-FORWARD CONTROL SYSTEM:

Another type of regulatory process frequently used in conjunction with negative-feedback systems is feed-forward control system. The temperature-sensitive nerve cells that trigger negative-feedback regulation of body temperature when body temperature begins to fall are located inside the brain. In addition, there are temperature-sensitive nerve cells in the skin, and these cells, monitor outside temperature. When outside temperature falls, these nerve cells immediately detect the change and relay this information to the brain, which then sends out signals to the blood vessels and muscles, resulting in heat conservation and increased heat production. *In this manner compensatory thermoregulatory responses are activated before the colder outside temperature can cause the internal body temperature to fall.* Thus, feed-forward regulation anticipates changes in a regulated variable (internal body temperature in this example), improves the speed of the body's

homeostatic responses, and minimizes fluctuations in the level of the variable being regulated.

Cerebellum corrects the cerebral mistakes before they are committed i.e. before the signals from cerebral cortex arrive in the anterior horn cells (AHC) of the spinal cord; cerebellum determines the degree of tone, extent and force of movement and thus makes the movements precise. Therefore, cerebellum coordinates movements by feed-forward control system. If cerebellum is diseased the movements become imprecise and inaccurate.

ACCLIMATIZATION:

The ability to adapt to a particular environmental stress is called acclimatization. If acclimatization is induced very early in life, however, at the critical period for development of a structure or response, it is termed a developmental acclimatization and may be irreversible e.g. the barrel-shaped chest of natives of the Andes mountains during the first few years of their lives by exposure to the low-oxygen environment of high altitude. The altered chest size remains even though the individual moves to a lowland environment later in life and stays there. Lowland persons who have suffered oxygen deprivation from heart or lung disease during their early years show precisely the same chest shape.

BIOLOGICAL RHYTHMS/CIRCADIAN RHYTHMS:

Many body functions undergo rhythmical changes. The most common example is the circadian rhythm; e.g. waking and sleeping, body temperature, hormone concentrations in the blood (fig.1.7), and excretion of potassium in the urine. Other cycles have much longer periods, the menstrual cycle (approximately 28 days) being the most well known.

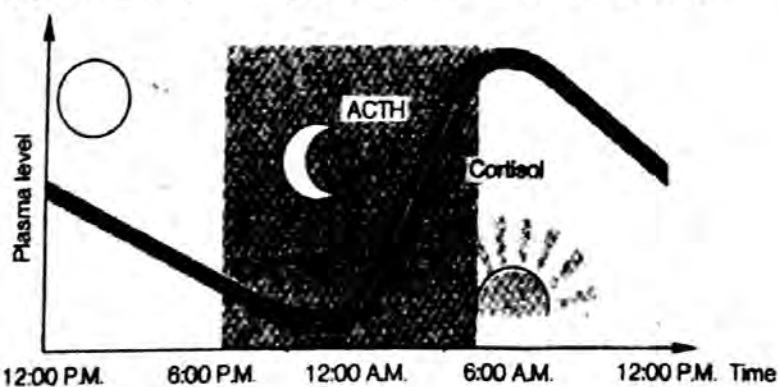


Fig. 1.7: Diurnal variation of ACTH and cortisol.

A crucial point concerning most body rhythms is that they are internally driven. Environmental factors do not drive the rhythm but rather provide the timing cues important for entrainment (i.e. setting of the actual hours) of the rhythm.

ISOLATION FROM EXTERNAL ENVIRONMENT:

The normal rhythm of sleeping and waking is subject to control by an internal clock i.e. circadian clock, the basis of which is not understood. The endogenous circadian sleep wake cycle usually of 24 hours, synchronizes with external day (light) and night (dark) cycle of 24 hours. With total isolation the circadian sleep-wake cycle becomes of 25 hours (in persons living in windowless cells, caves and underground rooms) due to temporary disturbance in synchronization between circadian clock and external 24 hours periodicity, which may last several days (fig.1.8).

EXPERIMENTAL EVIDENCE OF INTERNAL BIOLOGICAL CLOCK:

Subjects were put in experimental chambers; this completely isolated them from the external environment. For the first few days, they were exposed to a 24 hours rest-activity cycle in which the room lights were turned on and off at the same time each day. Under these conditions, their sleep-wake cycles were 24 hours long. Then, all environmental time cues (hints) were eliminated, and the individuals were allowed to control the lights themselves. Immediately, their sleep-wake patterns began to change. On the average, bedtime began about 30 min later each day and so did the wake-up time. Thus a sleep-wake cycle persisted in the complete absence of environmental cues, and such a rhythm is called a free-running rhythm. In this case it was approximately 25 hours rather than 24; that is, cues (hints) are required to entrain a circadian rhythm to 24 hours.

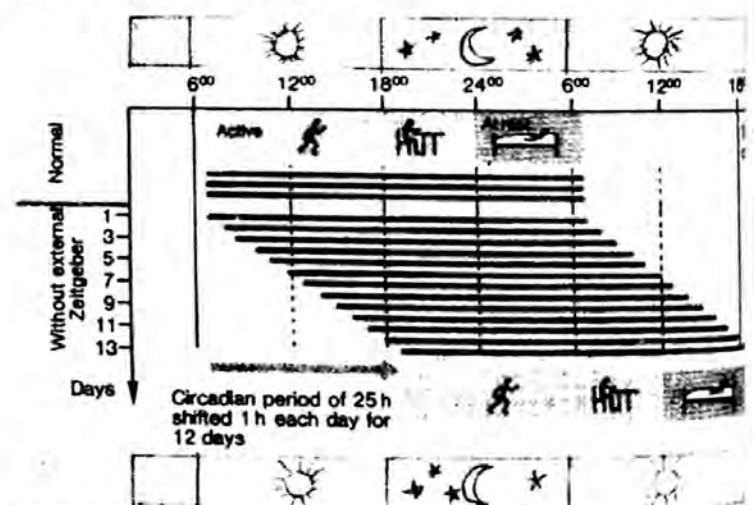


Fig. 1.8: Internal biological clock and circadian periods.

It is important to mention that by altering the duration of the light-dark cycles, sleep-wake cycles can be entrained to any value between 23 and 27 hours, but shorter or longer duration cannot be entrained (drag along). Because of this, the people whose work causes them to adopt sleep-wake cycles longer than 27 hours are never able to make the proper

adjustments and achieve stable rhythms. The result is symptoms similar to those of jet lag.

JET-LAG:

Environmental time cues (hints) also function to phase-shift rhythms, in other words, to reset the internal clock. Thus if one jets west or east to different time zone, the sleep-wake cycle and other circadian rhythms slowly shift to the new light-dark cycle. These shifts take time however, and the disparity between external time and internal time is one of the causes of the symptoms of jet lag i.e. disruption of sleep, gastrointestinal disturbances, decreased vigilance and attention span, and a general feeling of malaise (fig.1.8).

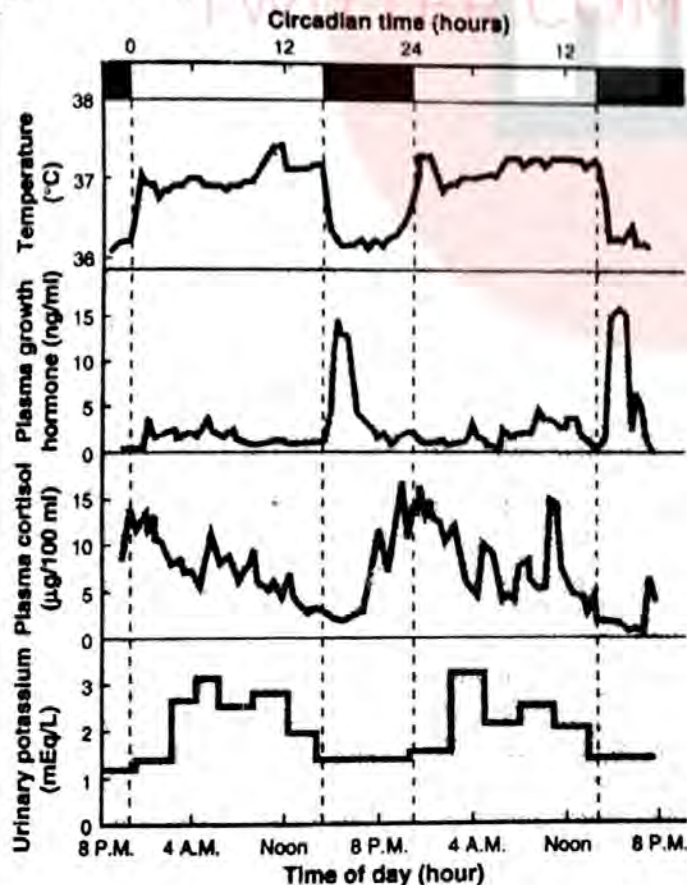


Fig. 1.9: Circadian rhythms; Temperature, growth hormone, cortisol and potassium.

SHIFT WORKERS:

Similar symptoms, which occur in jet-lag, also occur in workers on permanent or rotating night shifts. Such individuals generally do not adapt to these schedules even after several years because they are exposed to the usual outdoor light-dark cycle (normal indoor lighting is too dim to function as a good entrainer). In recent experiments, night-shift workers were exposed to extremely bright indoor lighting while they worked, and 8 hours of total darkness during the day while they slept. This

schedule produced total adaptation to the night-shift work within 5 days.

What is the neural basis of body rhythms? In the part of the brain called the hypothalamus are several specific collections of nerve cells that function as the principal pacemaker (time clock) for circadian rhythms. How they "keep time" independent of any external environmental cues is not really understood. The pacemaker receives input from the eyes and many other parts of the nervous system mediate the entrainment effects exerted by the external environment.

Biological rhythms enable homeostatic mechanisms to be utilized immediately and automatically by activating them at times when a challenge is likely to occur but before it actually does occur. For example, there is a rhythm in the urinary excretion of potassium such that excretion is high during the day and low at night; this makes sense since we ingest potassium in our food during the day, not at night when we are asleep (fig.1.9).

SIGNIFICANCE OF CIRCADIAN RHYTHMS:

Certain diseases have characteristic rhythms; e.g., heart attacks are almost twice as common in the first hours after awaking, and asthma frequently flares at night. This is also important for drug therapy e.g., once-a-day, timed-release pills for asthma are taken at night and deliver a high dose of medication between midnight and 8 A.M. perhaps the most striking application in medicine of the growing information about rhythms is in the treatment of cancer. Many drugs used in cancer chemotherapy kill only dividing cells; since cancer cells generally divide rapidly, they are preferentially destroyed. However, the drugs also injure normal tissues and organs consisting of cells that divide rapidly, leading to toxic side effects such as diarrhoea caused by damage to the intestinal lining. It is known that intestinal cells divide most slowly during the evening, and so by delivering the drug only at this time, a much larger dose of the drug can be given with less toxicity to these normal cells.

AGING AND HOMEOSTASIS:

Aging is associated with a decrease in the number of cells in the body, due to combination of decreased cell division and increased cell death, and to malfunction of many of the cells. The immediate cause of these changes is probably an interference in the function of the cell's macromolecules (DNA, RNA, and cell proteins) and in the flow of information between these macromolecules. The crucial question, unanswered at present, concerns what causes these changes. One theory places the blame on progressive accumulation of damage to the

macromolecules, while the others hypothesize that cellular senescence is actually programmed in our genes; certain genes responsible for the "aging process" become activated as one grows older.

FREE RADICAL THEORY:

Free radicals are electrically charged molecules that have an un-paired electron called a *superoxide* (fig. 1.10). Such molecules are unstable and highly reactive. A free radical produces oxidative damage in a nearby lipid, protein or nucleic acid by stealing an electron to accompany its un-paired electron. The damage done by these super-oxides are wrinkled skin, stiff joints and hardened arteries.

Dietary substances such as vitamin E, vitamin C, beta-carotene, and selenium are anti-oxidants that inhibit free radical formation.



(a) Oxygen molecule

(b) Superoxide free radical

Fig. 1.10: Super oxide free radical.

1. The physiological manifestations of aging are a gradual deterioration in the function of virtually all tissues and organ systems and in the capacity of the body's homeostatic systems to respond to environmental stress. To take another example, a similar re-evaluation of changes in heart function with age has suggested that much of the decrease in the ability of the heart to pump blood at rest and during exercise in older people may be the result of disease and lifestyle changes (decreased physical activity, for example) rather than to the aging process itself. In contrast, the 30 – 40 percent decrease (some-what less in women) in the mass and strength of limb muscles that occurs in men between 30 and 80 years of age is due to aging changes. Physically active individuals have greater strength at any given age, compared to inactive persons, but the rate of decline with age is similar.

2. The human life span, nowadays most commonly 70 – 80 years, can be viewed as a combination of maturation and deterioration of "build-up" and "run-down". Although the two processes coexist, maturation (including both physical growth and increasing skills) dominates in the first two to three decades and deterioration dominates in the last two to three decades of life (fig. 1.11).

MATURATION:

The major growth in body tissues takes place in about first 15 years of life. Physical performance

tends to improve for a further similar period, with increasing muscle strength, particularly in the male, and this function can continue to improve with experience and even centenarians can experience and participate in new activities.

Throughout the "life-span" much of this maturation is due to developments in the brain and this is highly relevant in regard to the special senses. Large regions of the brain are concerned with the interpretation of patterns obtained from the eyes and from the ears. These regions are organized during maturation and contribute in turn to our ability to carry out skilled physical activities and make appropriate judgements. There is increasing evidence that localized brain regions are involved in critical decisions. Such evidence is provided by modern scanning techniques, which can, for example, show increased activity in a specific area when people are matching patterns with different colours. Further evidence comes from patients with small cerebral tumours whose only symptoms may be loss of a specific skill, i.e. the skill to identify paintings by specific artists.

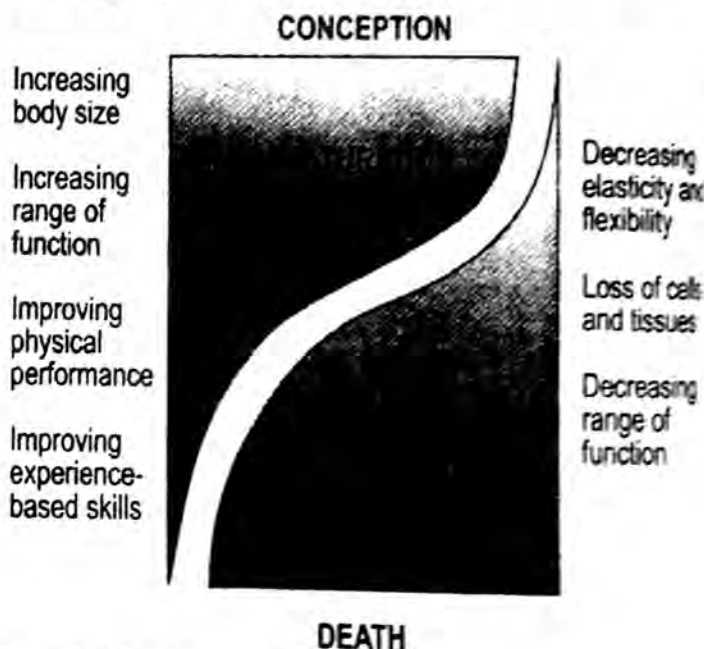


Fig. 1.11: Maturation and deterioration.

DETERIORATION:

As indicated in figure 1.11, deterioration occurs to some extent even in the foetal state and infancy, e.g. loss of elasticity and flexibility with gradual drying out of the body and deterioration in major body components such as collagen and elastin. With increase in age, the effects of loss of irreplaceable cells and tissues, e.g. brain cells, teeth, cartilage, becomes apparent, leading to a severe decrease in the ability to vary function in old age. This may range from "less ability" to deal with the fluid loss due to intestinal infections to "increased vulnerability" to

excessive heat and cold. This diminishing range of functions is also evident in the special senses.

The causes of the deterioration are the subject of much research, and may include cell self-destruction "apoptosis" and accumulation of toxins, including the currently fashionable oxygen free radicals (super oxide). In more general terms, some of the major causes of accelerated aging, or deterioration, are environmental and, to some extent, preventable e.g. cigarette smoke, radiation, including solar radiation, and in the case of hearing overuse in the form of sustained loud noise and music.

PRINCIPLES OF CELL PHYSIOLOGY

INTRODUCTION:

The human cell has three principal parts: nucleus, cytoplasm and outer membrane. The nucleus, the "executive" part of the cell, governs structure, so that cells produce only exact copies of themselves. Lung cells make only lung cells, kidney cells only kidney cells. Cytoplasm is the jelly-like substance in which all the important nucleus floats; it controls cellular respiration, growth, and waste disposal. Enclosing the entire cell is the gossamer (fine) membrane, which acts as a molecular sieve. Through it, nourishment passes into the cell to be distributed by a minute system of canals and through the same membrane wastes are passed outward for disposal.

One of the most fascinating features of cells is their potential immortality. In 1912, the late Alexis Carrel of the Rockefeller Institute in New York snipped out a piece of chicken heart. Periodically it was fed nourishing broth, and from time to time excess tissue was trimmed away. The cells remained alive for thirty-four years; and were permitted to die only when the experiment had fulfilled its usefulness.

In general, cells have two main lines of responsibility: their own housekeeping activities and their community responsibilities. The first includes such functions as eating and waste disposal. The second includes the responsibility of each cell to all others.

Tiny cells in the pancreas, for example, produce minute squirts of the insulin which control sugar used by all other cells; fat cells store droplets of oil to be used as fuel to warm the rest of the body; stomach cells manufacture enzymes which aid in protein digestion.

ORIGIN OF CELLS:

The cell is the smallest structural unit of living organism. All cells are basically similar in their

chemical composition. The activity of an organism is the sum of activities and interactions of its cells.

Cells are divided into two main classes, initially defined by whether, they contain a nucleus or not. Prokaryotic cells (bacteria) lack nuclear envelope; while eukaryotic cells have a nucleus in which the genetic material is separated from the cytoplasm.

No.	Characteristics	Prokaryote	Eukaryote
1.	Nucleus	Absent	Present
2.	Diameter of a typical cell	1 μm	10 – 100 μm
3.	Cytoskeleton	Absent	Present
4.	Cytoplasmic organelles	Absent	Present
5.	Chromosomes	Single circular DNA molecules	Multiple linear DNA molecules

Table 1.1: Prokaryotic Vs eukaryotic Cells.

EUKARYOTIC CELLS:

Like prokaryotic cells, all eukaryotic cells are surrounded by plasma membrane and contain ribosomes. However, eukaryotic cells are much more complex and contain a nucleus, a variety of cytoplasmic organelles, and a cytoskeleton. The largest and most prominent organelle of eukaryotic cells is the nucleus, with a diameter of approximately 5 μm . The nucleus contains the genetic information of the cell, which in eukaryotes is organized in a linear rather than circular DNA molecules. The nucleus is the site of DNA replication and of RNA synthesis; the translation of RNA into proteins takes place on ribosomes in the cytoplasm (fig.1.12)

In addition to a nucleus, eukaryotic cells contain a variety of membrane-enclosed organelles within their cytoplasm (table 1.1). These organelles provide compartments in which different metabolic activities are localized. Eukaryotic cells are generally much larger than prokaryotic cells.

Mitochondria, which are found in almost all eukaryotic cells, are the sites of oxidative metabolism and are thus responsible for generating most of the ATP derived from the break down of organic molecules.

Lysosomes and peroxisomes also provide specialized metabolic compartments for the digestion of macromolecules and for various oxidative reactions, respectively.

Two cytoplasmic organelles, the endoplasmic reticulum and the Golgi apparatus, are specifically devoted to the sorting and transport of proteins

destined for secretion, incorporation into the plasma membrane, and incorporation into lysosomes.

Eukaryotic cells have another level of internal organization: the cytoskeleton, a network of protein filaments extending throughout the cytoplasm. The cytoskeleton provides the structural framework of the cell, determining cell shape and the general organization of the cytoplasm. In addition, the cytoskeleton is responsible for the movements of entire cells (e.g., the contraction of muscle cells) and for the intracellular transport and positioning of organelles and other structures, including the movements of chromosomes during cell division.

We can divide a cell into four principal parts:

1. PLASMA MEMBRANE:

It is the outer, limiting membrane separating the cell's internal components from the extra-cellular materials and external environment.

2. CYTOSOL:

The thick, semi-fluid intracellular fluid is termed the cytosol. The cytosol contains many dissolved proteins and enzymes, nutrients, ions, and other small molecules, which all participate in various phases of metabolism. Organelles and inclusions

are suspended in the cytosol. The term cytoplasm includes cytosol, all organelles (except the nucleus) and inclusions.

3. ORGANELLES:

Highly organized structures with characteristic shapes that are specialized for specific cellular activities. The organelle with the largest volume is the nucleus, which contains most of a cell's genetic material.

4. INCLUSIONS:

Temporary structures in the cytoplasm that contain secretions and storage products of the cell.

PLASMA MEMBRANE/CELL MEMBRANE:

The thin barrier that separates the internal components of a cell from extra-cellular materials is the plasma membrane, also called the cell membrane. The plasma membrane is the gatekeeper that regulates passage of substances into and out of the cell.

The fluid mosaic model of membrane structure describes the molecular arrangement of the plasma membrane and other membranes in living organisms. A mosaic is a pattern of many small

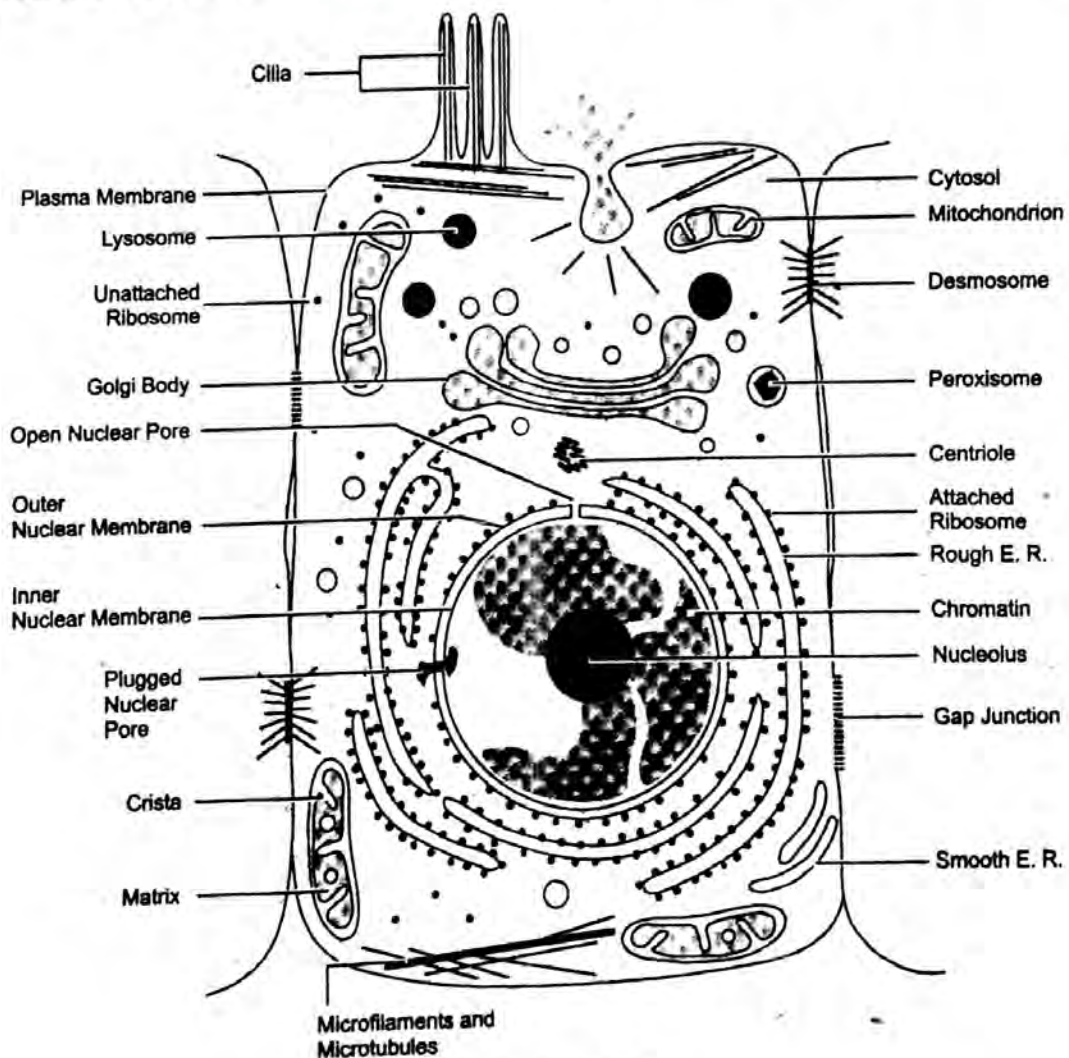


Fig. 1.12: A typical cell.

pieces fitted together. According to this model, the membrane is a mosaic of proteins floating like icebergs in a sea of lipids (fig. 1.13).

MEMBRANE CHEMISTRY AND ANATOMY:

Plasma membranes of typical animal cells are about a 50:50 mix by weight of proteins and lipids that are held together by non-covalent interactions. Since proteins are larger and more massive than lipids, however, there are about 50 lipid molecules for each protein molecule.

MEMBRANE CARBOHYDRATES:

The membrane carbohydrates occur almost invariably in combination with proteins and lipids in the form of glyco-proteins and glyco-lipids. The carbohydrate compounds like proteoglycans, which are mainly carbohydrate substances bound together by small protein cores, often are loosely attached to the outer surface of the cell as well. Thus the entire outside surface of the cell often has a loose carbohydrate core called the glycocalyx.

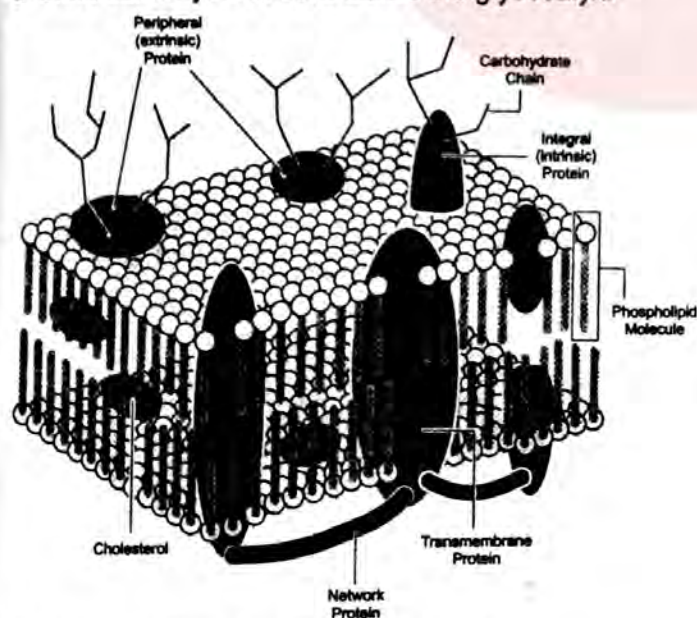


Fig. 1.13: Fluid mosaic model of cell membrane.

FUNCTIONS OF GLYCOCALYX:

1. Some membrane carbohydrates function as receptor substances for binding hormones like insulin and in doing so activate attached internal proteins.
2. The glycocalyx of some cells attaches to the glycocalyx of other cells, thus attaching the cells to one another.

The carbohydrate moieties of glycocalyx may serve to modify the electric charge at its surface.

MEMBRANE LIPIDS:

About 75% of the lipids are phospholipids i.e., lipids that contain phosphorus. Present in smaller amounts are cholesterol and glycolipids, which are lipids with

one or more sugar groups attached. The phospholipids line up in two parallel layers forming a phospholipid bilayer. This arrangement occurs because the phospholipids are amphipathic (amphi = on both sides, double; pathos = feeling). Amphipathic molecules have a dual nature; they contain both polar parts, which are the phosphate containing "heads," which are hydrophilic (water loving). The non-polar parts are the two fatty acid "tails," which are hydrophobic (water fearing). The molecules orient in the bilayer in such a way so that the heads face outward on either side, toward the watery cytosol and extra-cellular fluid. The tails face each other in the membrane's interior. The bilayer forms the basic framework of the plasma membrane (fig. 1.14).

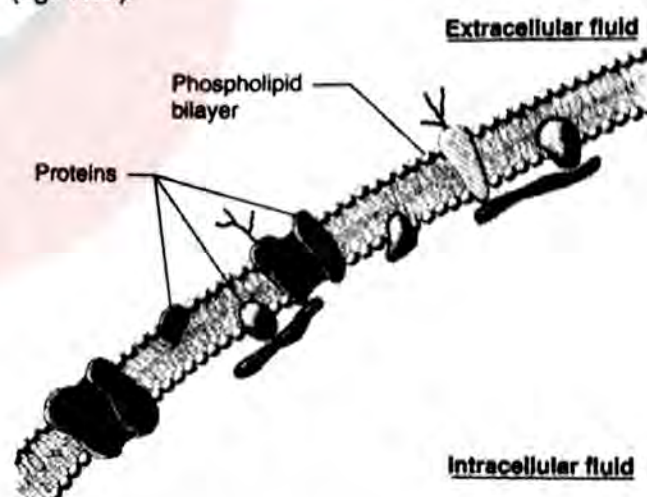


Fig. 1.14: Cell membrane; Phospholipid bilayer.

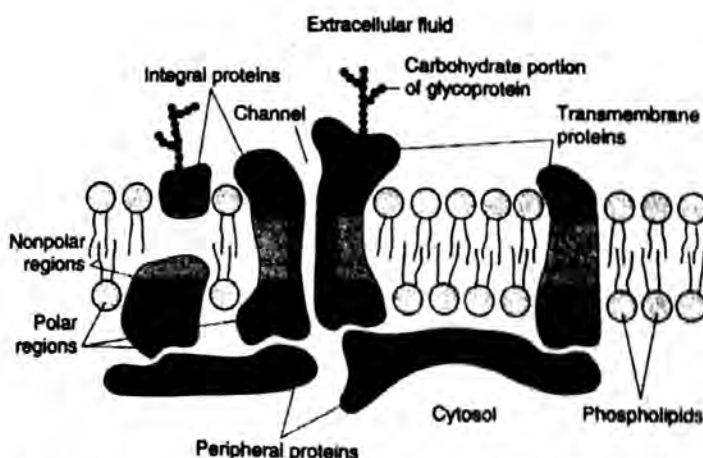


Fig. 1.15: Membrane chemistry; carbohydrates, lipids and proteins.

The cholesterol molecules in the membrane are also lipid in nature, because their steroid nucleus is highly fat-soluble. These molecules are resolved in the phospholipid bilayer of the membrane. They mainly help to determine the degree of permeability

of the bilayer to water-soluble constituents of the body fluids. The cholesterol controls much of the fluidity of the membrane as well (1.15).

MEMBRANE PROTEINS:

Proteins are the other major constituents of cell membranes, constituting 25 to 75% of the mass of the various membranes of the cell. The membranes behave as a fluid mosaic in which proteins are inserted into a lipid bilayer. While phospholipids provide the basic structural organization of membranes, the membrane proteins carry out the specific functions of the different membranes of the cell. These proteins are divided into two general classes, based on the nature of their association with the membrane. *Integral membrane proteins* are embedded directly within the lipid bilayer. *Peripheral membrane proteins* are not inserted into the lipid bilayer but are associated with the membrane indirectly, generally by interactions with integral membrane proteins (fig. 1.15).

Most integral membrane proteins (called trans-membrane proteins) span the lipid bilayer, with portions exposed on both sides of the membrane. Like the phospholipids, trans-membrane proteins are amphipathic molecules, with their hydrophilic portions exposed to the aqueous environment on both sides of the membrane.

The selective permeability of biological membranes to small molecules allows the cell to control and maintain its internal composition. Only small uncharged molecules can diffuse freely through phospholipid bilayers. Small nonpolar molecules, such as oxygen and carbon dioxide are soluble in the lipid bilayer and therefore can readily cross cell membranes.

Channel proteins form open pores through the membrane, allowing the free passage of any molecule of the appropriate size. Ion channels, for example, allow the passage of inorganic ions such as Na^+ , K^+ , Ca^{++} , and Cl^- across the plasma membrane. Once open, channel proteins form small pores through which ions of the appropriate size and charge can cross the membrane by free diffusion. The pores formed by these channel proteins are not permanently open; rather, they can be selectively opened and closed in response to extra-cellular signals, allowing the cell to control the movement of ions across the membrane. Such regulated ion channels have been particularly well studied in nerve and muscle cells, where they mediate the transmission of electrochemical signals.

The *carrier proteins* selectively bind and transport specific small molecules, such as glucose. Rather than forming open channels, carrier proteins act like

enzymes to facilitate the passage of specific molecules across membranes. In particular, carrier proteins bind specific molecules and then undergo conformational changes that open channels, through which the molecules to be transported can pass across the membrane and be released on the other side. The molecules can be transported in an energetically unfavourable direction across a membrane (e.g., against a concentration gradient); their transport in that direction is coupled to ATP hydrolysis as a source of energy; a process called active transport. The free energy stored as ATP can thus be used to control the internal composition of the cell, as well as to drive the biosynthesis of cell constituents.

The *ion pumps* responsible for maintaining gradients of ions across the plasma membrane provide important examples of active transport driven directly by ATP hydrolysis. The concentration of Na^+ is approximately ten times higher outside than inside of cells, whereas the concentration of K^+ is higher inside than out. These ion gradients are maintained by the $\text{Na}^+ - \text{K}^+$ pump (also called the $\text{Na}^+ - \text{K}^+$ ATPase), which uses energy derived from ATP hydrolysis to transport Na^+ and K^+ against their electrochemical gradients. This process is a result of ATP-driven conformational changes in the pump.

PHYSIOLOGICAL PUMPS:

A physiological pump or biological pump is an active transport mechanism that moves molecules or ions through cell membranes in an uphill direction, i.e. against concentration gradient.

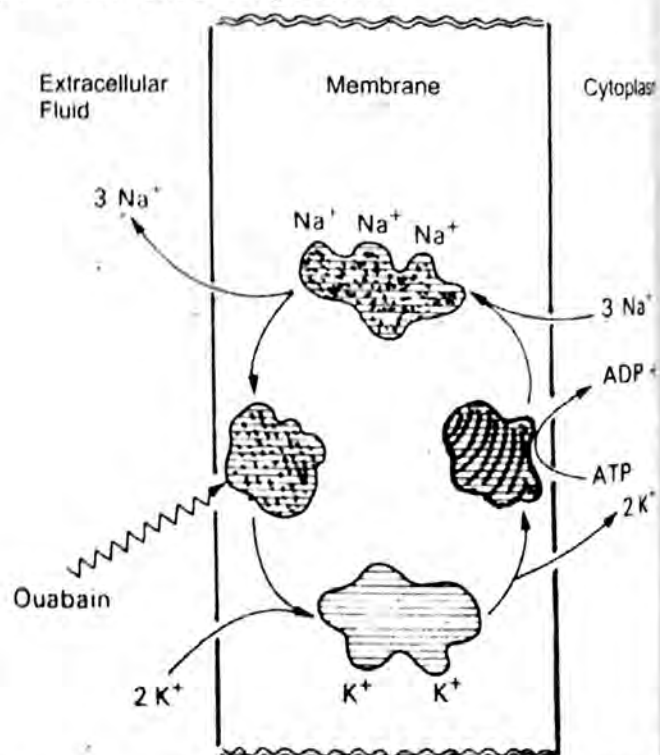


Fig. 1.16: Simple carrier model of $\text{Na}^+ - \text{K}^+$ exchange pump in cell membranes.

SODIUM POTASSIUM PUMP:

In almost all tissues, the $\text{Na}^+ - \text{K}^+$ pump is responsible for the coupled active transport of Na^+ out of the cells and K^+ into the cells. The pump extrudes 3 Na^+ from the cell for 2 K^+ it takes into the cell i.e. it has a coupling ratio of 3:2 (fig 1.16).

Sodium-potassium pump is a unique protein in the cell membrane. This protein is adenosine triphosphatase i.e. an enzyme that catalyses the hydrolysis of ATP to ADP and it is activated by Na^+ and K^+ . The ATP provides energy for transport.

EVENTS OF SODIUM PUMP:

1. SODIUM BINDING:

In the cytoplasm of a cell, $\text{Na}^+ - \text{K}^+$ ATPase react to bind Na^+ in the presence of Mg^{++} , Na^+ , ATP and transfers terminal PO_4^- of ATP to it (to enzyme).

2. PHOSPHORYLATION OF ATPase:

Phosphorylation of the enzyme ATPase activates $\text{Na}^+ - \text{K}^+$ pump, changing its shape, so that its sodium binding site faces the opposite direction i.e. towards the outside of the cell.

Na^+ binding is associated with phosphorylation of the protein and 2 K^+ binding with dephosphorylation.

UNBINDING OF Na^+ AND BINDING OF K^+ :

3. With the sodium-binding site on the ATPase now facing outward, sodium unbinds from the enzyme and enters the ECF, as does phosphate. Immediately following the unbinding of Na^+ from the enzyme, K^+ in the ECF binds to it.

4. SCHUFFLING OF ATPase:

The enzyme then changes back to its original shape that is, with its Na^+ binding site facing the cytoplasm inside the cell, and releases the potassium into it.

The sodium-potassium transport mechanism illustrates certain features believed to characterize all active transport mechanisms and distinguishes them from passive mechanisms. An enzyme located in a cell membrane is postulated to serve as a carrier that combines with a substance and transports it through the membrane (fig. 1.17).

5. GENESIS OF RMP:

In essence, the outward diffusion of K^+ down its concentration gradient (created by $\text{Na}^+ - \text{K}^+$ pump) develops the resting membrane potential.

6. DEPOLARISATION OF MEMBRANE:

Anything that interrupts the active transport of sodium and potassium is soon followed by both the equilibration of ions and electric charges on the two sides, and depolarises the membrane.

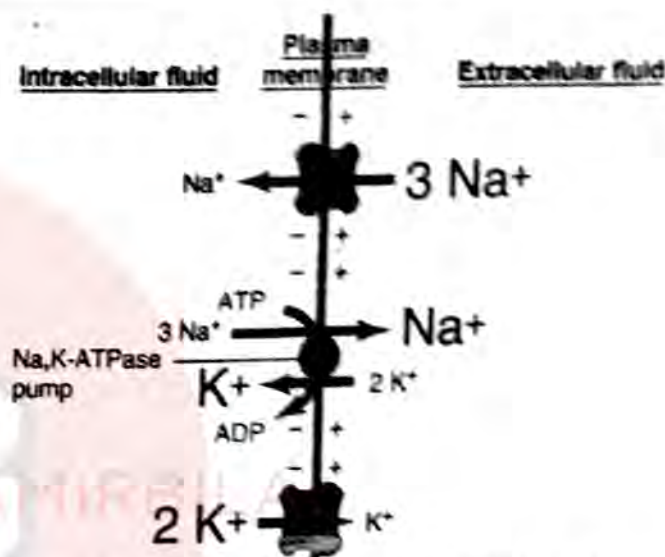


Fig. 1.17: $\text{Na}^+ - \text{K}^+$ ATPase pump exchanges 3Na^+ for 2K^+ .

EXPERIMENTAL EVIDENCES:

1. LOADING OF RADIO-ACTIVE SODIUM:

Experiment on squid (giant) axon:- A squid giant axon is loaded with radioactive Na^+ by soaking or by injection; so that radioactive Na^+ goes into the axon. The axon is then placed in sea water. The rate of efflux of radio-active Na^+ is measured. It proves that the sodium pump actively discharges Na^+ out of the axon.

2. INHIBITION OF OXIDATIVE METABOLISM:

If some inhibitor of oxidative metabolism e.g. cyanide, dinitrophenol, or ouabain is added to the sea water, which is bathing the axon. The rate of sodium efflux falls dramatically. This clearly shows that sodium pump is inhibited.

3. ATP INDUCED EFFLUX:

The efflux i.e. extrusion of Na^+ may be partially restored by injection of compounds containing high-energy phosphate bonds e.g. ATP into the axon. It means when energy is supplied the pump once again starts working.

4. PRESENCE OF ECF K^+ :

Sodium pump is in part dependent on presence of some extra-cellular fluid potassium. If extra-cellular fluid (ECF) contains no potassium, Na^+ efflux is reduced dramatically, although some efflux does continue. It is reported that sodium is in part exchanged for K^+ .

FUNCTIONS OF $\text{Na}^+ - \text{K}^+$ PUMP:

ELECTROGENICITY:

Since $\text{Na}^+ - \text{K}^+$ ATPase transports 3 Na^+ out of the cell for each 2 K^+ in the cell. It is an electrogenic pump i.e. it produces net movement of positively charged ions out of the cell and creates a polarized membrane i.e. negativity inside.

THE THERMOGENICITY (ENERGY) LIBERATION

Active transport of Na^+ and K^+ is one of the major energy consuming processes in the body and probably accounts for a large part of basal metabolism. 70% of the basal metabolic rate (BMR) is due to thermal energy liberation of this pump.

Furthermore, there is a direct link between Na^+ and K^+ transport and metabolism; the greater the rate of pumping, the more ATP is formed, and available supply of ATP determines the rate at which ATP is formed by oxidative phosphorylation.

STIMULATION OF Na^+ - K^+ PUMP

In hyperthyroidism, a type of hyperthyroidism Na^+ - K^+ pump is activated by the action of thyroxine (T_4). Consequently tissues become hyper-excitable and more thermal energy is liberated from the breakdown of ATP. This results in increased basal metabolic rate (BMR), increased body temperature and peripheral vasodilatation.

INHIBITION OF Na^+ - K^+ ATPase PUMP

Digitalis (Lanoxin) is a drug used in the congestive cardiac failure, because it strengthens and improves the myocardial function. Digitalis exerts its effect by inhibition of the Na^+ - K^+ pump, which lets more Na^+ to accumulate inside heart muscle cells. The result is a smaller Na^+ concentration difference across the membrane. In turn, the Na^+ - Ca^{++} antiporters slow down due to the smaller Na^+ concentration difference. As a result, more Ca^{++} remains inside heart muscle cells, and this increases the force of heart muscle contraction. As this example illustrates, the balance between the concentrations of Na^+ and Ca^{++} in the cytosol and extra-cellular fluid is crucial to the normal functioning of nerve and muscle cells.

CALCIUM PUMP

The active transport of Ca^{++} across the plasma membrane is driven by Ca^{++} pump that is structurally related to the Na^+ - K^+ pump and is similarly powered by ATP hydrolysis. The Ca^{++} pump transports Ca^{++} out of the cell, so intracellular Ca^{++} concentrations are extremely low. Small increases in intracellular Ca^{++} levels can modulate the cellular functions. Such transient, and highly localized increase in intracellular Ca^{++} play important roles in cell signalling.

The coordinated uptake of glucose and Na^+ is an example of symport, the transport of two molecules in the same direction. In contrast, the facilitated diffusion of glucose is an example of uniport, the transport of only a single molecule. Active transport can also take place by antiport, in which two molecules are transported in opposite directions, e.g. Ca^{++} is exported from cells not only by the Ca^{++}

pump but also by the Na^+ - Ca^{++} antiporter that transports Na^+ into the cell and Ca^{++} out. Another example is provided by the Na^+ - H^+ exchange protein, which functions in the regulation of intracellular pH. The Na^+ - H^+ antiporter couples the transport of Na^+ into the cell with the export of H^+ thereby removing excess of H^+ ions produced by metabolic reactions and preventing acidification of the cytoplasm.

MEMBRANE PHYSIOLOGY:

Plasma membrane determines the composition of cell. It protects the cell from changes in internal environment but only within physiological range. It acts as a homeostatic organ in this respect maintaining an optimum concentration of substances within the cell; and controlling volume of fluid within the cell; distribution of ions, passage of oxygen and carbon-dioxide. All biochemical phenomena can be brought ultimately to a membrane dimension; whether it is inter-action of cancer cells, transduction of energy, cell division, or immuno-chemical reactions.

ELECTROCHEMICAL GRADIENT:

The plasma membrane encloses the cellular contents and separates them from the extra-cellular fluid or, sometimes, from the external environment. The membrane maintains an electrical and chemical gradient (difference), called an electrochemical gradient, between the inside and outside of the cell. The chemical portion of the electrochemical gradient arises because the membrane maintains different chemical compositions in the cytosol and in extra-cellular fluid. The chemicals other than ions are present in different concentrations inside and outside living cells. In ECF, the main cation (positively charged ion) is Na^+ and the main anion (negatively charged ion) is chloride (Cl^-). In the cytosol, the main cation is K^+ , while the two dominant anions are organic phosphates (PO_4^- groups attached to organic molecules such as ATP) and negatively charged proteins.

VOLTAGE ACROSS THE MEMBRANE:

The electrical gradient arises because the inside surface of the membrane is more negatively charged than that outside surface in most cells. As a result, there is a voltage called the membrane potential across the membrane. Voltage is a form of potential energy that occurs when positive and negative charges are separated; examples of such charge separation are found in ordinary flashlight and car batteries. In living cells, a small separation of ions (charged particles) by the membrane gives rise to the membrane potential. This separation of charges occurs only near the plasma membrane. Overall,

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both the cytosol and extra-cellular fluid are electrically neutral; if all the positive and negative charges are added up in each fluid, they would balance except in a thin region adjacent to the membrane. The voltage across the plasma membrane of cells throughout the body usually is between -20 and -200 millivolts (mV). (One mV is one-thousandth of a volt = 0.001 V). The negative sign in front of the number means that the inside is negative relative to the outside. Under certain conditions, some cells exhibit a positive membrane potential. The electrochemical gradient and the resulting membrane potential are important for the proper functioning of most cells.

SELECTIVE PERMEABILITY:

The plasma membrane regulates entry and exit of materials. It permits passage of certain substances and restricts the passage of others. This property of membrane is called selective permeability.

A membrane is said to be permeable to a substance if it allows the free passage of that substance. Although plasma membranes are not completely permeable to any substance, they do permit some substances to pass more readily than others. Water, for example, usually passes more easily than most other substances. The selective permeability of a plasma membrane to different substances depends on several factors that relate to the structure of the membrane.

GENESIS OF MEMBRANE POTENTIAL:

The distribution of ions across the cell membrane and the nature of this membrane provides the explanation for membrane potential (MP). K^+ diffuses out of the cell along its concentration gradient, while non-diffusible anion components stay in the cell, creating a potential difference across the membrane. There is thus a slight excess of cations outside and a slight excess of anions inside the membrane. It should be emphasized however, that the number of ions responsible for membrane potential is a minute fraction of the total number present.

The ionic pumps and associated metabolic activity maintain the steady state ionic gradients across the nerve cell membrane and are necessary in the long run.

The restorative processes of sodium inactivation and K^+ efflux (tends to maintain the membrane potential at the original un-excited state) must be opposed by very large depolarisation in order to get sufficient sodium influx to start regeneration.

PRINCIPLES OF CELL HOMEOSTASIS:

1. Water is in general in osmotic equilibrium across the cell and easily passes back and forth across them.
2. Large internal organic molecules both charged and uncharged are retained within the cell.
3. The osmotically active organic molecules held within the cell by the cell membrane, must be balanced by the external presence of some substances (i.e. sodium).
4. The charge on the internal organic ions is in the aggregate negative, and some cation must be present to give electro-neutrality within the cell. The predominant intracellular cation is potassium.
5. There is a negative *potential difference* between the inside and outside of the cell. The negative, membrane potential is due to the tendency of *potassium ions*, to equalize its internal and external concentration by diffusing out of the cell. The effect of negative membrane potential is to exclude negative ions, particularly chloride from the cell interior, while accelerating the slow tendency of sodium to equalize its internal and external concentrations by diffusing into the cell.
6. To prevent slow net inward movement of Na^+ , cells utilize metabolic energy to transport or pump the excess sodium out of the cell.

CHARACTERISTICS OF CELL MEMBRANE:

1. Cell membranes are thin and have a diameter of 70 – 100 $\text{\AA}$.
2. Cell membranes are electric insulators.
3. Cell membranes contain carrier molecules, channel proteins, receptors and various mixtures of lipids.
4. Cell membranes allow small molecules and lipid soluble substances to pass through easily, while charged molecules and large molecules do not pass easily.
5. Portions of cell membranes are specialized for transport of ions and hence excitation, conduction and metabolism etc.
6. Cell membranes are polarized i.e. they have a charge on them.

CELL METABOLISM:

It is the sum of all the catabolic and anabolic reactions in the cell. The breakdown of carbohydrates, lipids, and proteins releases energy that is used to synthesize ATP. The ATP molecules are small packets of energy that are used to drive chemical reactions and processes such as active transport.

The production of ATP takes place in the cytosol and mitochondria through a series of chemical reactions. Energy from food molecules is transferred to ATP in a controlled manner. If energy in food molecules is released at once, the cell literally would burn.

Once glucose is transported into the cell, a series of reactions take place within the cytosol.

These chemical reactions called as glycolysis, convert the glucose into pyruvic acid. Pyruvic acid can enter different biochemical pathways, depending on oxygen availability.

AEROBIC RESPIRATION:

Aerobic respiration occurs when oxygen is available. The pyruvic acid molecules enter mitochondria and through another series of chemical reactions collectively called as citric acid cycle and the electron transport chain, are converted into carbon dioxide and water (fig. 1.18).

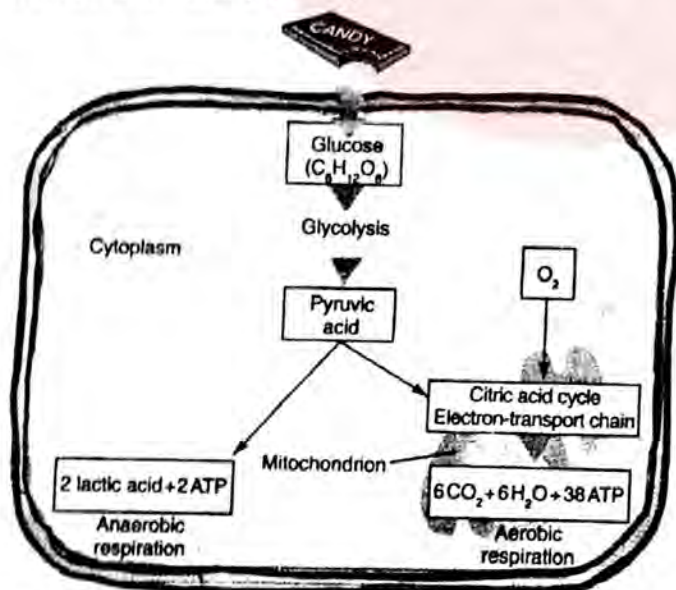


Fig. 1.18: Overview of cell metabolism.

CHARACTERISTICS OF AEROBIC RESPIRATION:

1. Aerobic respiration can produce 36-38 molecules of ATP from one molecule of glucose.
2. Aerobic respiration requires oxygen. Without oxygen aerobic respiration is inhibited; and cells don't produce enough ATP to sustain life.
3. During aerobic respiration carbon atoms of food molecules are separated from one another to form carbon dioxide. Thus the carbon dioxide, which is breathed out, comes from the food we eat.

ANAEROBIC RESPIRATION:

1. It occurs without oxygen and includes the conversion of pyruvic acid to lactic acid.
2. There is a net production of 2 ATP molecules for each glucose molecule used.

3. During intense exercise when aerobic respiration has depleted the oxygen supply, anaerobic respiration can provide additional ATP for short periods.

CELL COMMUNICATION:

The endocrine and nervous systems depend on chemical signals for their function. Inter-cellular chemical signals facilitate one cell to communicate with another. These signals co-ordinate and regulate the activities of most cells. Neuro-transmitters and neuro-modulators are inter-cellular chemical signals that play important roles in the function of the nervous system. Hormones are chemical signals secreted by endocrine glands. This includes interactions with other body cells, foreign cells, and legends such as hormones, neurotransmitters, enzymes, nutrients, and antibodies in the extra-cellular fluid.

Cells have developed special forms of communication that permit specific and detailed communication to be passed between them. Nerve cells communicate with each other over short distances by releasing specific chemical transmitters. Chemical messengers can also act over long distances in the human body. Hormones are released into the blood stream by the endocrine glands and are transported throughout the body.

WHAT IS A HORMONE?

The definition of a hormone has been complicated by a number of discoveries resulting in recognition of various molecules acting as autocrine, paracrine, and neurocrine.

AUTOCRINE REGULATORS:

When the molecules are produced and act within the same tissues of an organ are called autocrine regulators. For example, nor-adrenaline released from nerve endings modulates the release of the same substance from neighbouring nerves. Similarly cytokines produced by lymphocytes regulate different cells of immune system.

PARACRINE REGULATORS:

These are molecules produced within one tissue that regulate a different tissue of the same organ. For example, testosterone produced in the testes promotes spermatogenesis. Similarly nitric oxide produced in the endothelium of blood vessels causes the dilatation of blood vessels by acting on the smooth muscles.

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These are molecules produced by nerve cell bodies by the process of neuro-secretion, thrown into the circulation and regulate a distant organ. An example

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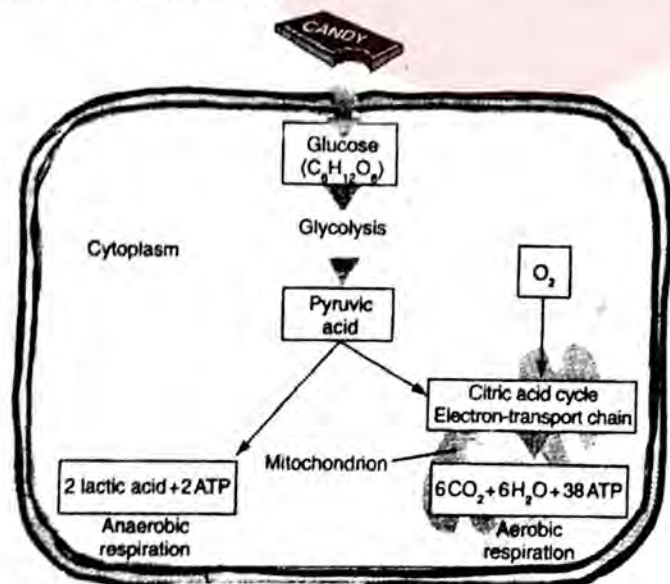


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of a neurocrine substance is ant-diuretic hormone (ADH), produced by the neurons of hypothalamus, stored in the nerve terminals in the posterior pituitary, secreted into the general circulation, and exerts its action on the kidney (renal tubules), leading to reabsorption of water. Ultimately less urine is formed (anti-diuresis)

NEURO-MODULATORS:

Neuro-modulators are hormones, neuro-peptides and other messengers that modify synaptic transmission. They may stimulate a neuron to raise or lower the number of receptors in the post-synaptic membrane, thus adjusting its sensitivity to a neuro-transmitter. The neuro-modulators may alter the rate of neuro-transmitter synthesis, release, re-uptake or break down. Opioids modulate pain impulses by acting to reduce sensitivity to pain peripherally as well as centrally by activating opiate receptors in the peri-aqueductal grey area. Acupuncture is associated with the release of enkephalins into the cerebro-spinal fluid (CSF). A recent and surprising discovery is nitric oxide (NO), a light weight gas that is released by post-synaptic neurons in some areas of the brain concerned with learning and memory. Nitric oxide diffuses into the pre-synaptic neuron and stimulates it to release more neuro-transmitter. Thus there is at least some chemical communication that goes backward across a synapse.

NEURO-TRANSMITTERS:

Neuro-transmitters are small organic compounds, about the size of amino acids that function at the synapse. The criteria for a substance to be called as neuro-transmitter is that

It is synthesized in the cell body, transported to the nerve terminals, stored in the vesicles, released with an appropriate stimulus into the synaptic cleft, binds to the specific receptors on the post-synaptic cell and alters the physiology of the cell. Finally the neuro-transmitter is broken down into components and some of the broken down products are re-up taken by the neuron.

TYPICAL HORMONE:

A hormone is a chemical messenger synthesized by a cell or a group of cells or a pure or mixed endocrine gland; it is thrown directly into the circulation without the help of a duct, circulates bounded to proteins in micro-concentrations and acts at a distant tissue called its target tissue. In the target tissue it interacts with specific receptors to elicit specific effects involving the regulation of cellular activities.

CYTOSKELETON:

Cellular shape and the capability to carry out a variety of coordinated cellular movements depend on a complex internal network of filamentous proteins in the cytoplasm called the cytoskeleton. The cytoskeleton is responsible for movement of whole cells, such as phagocytes, and for movement of organelles and some chemicals within the cell. Three main types of protein filaments, microfilaments, microtubules, and intermediate filaments comprise the cytoskeleton.

Micro-filaments are rod-like structures of varying length that are formed from the protein actin. In muscle tissue, actin filaments (thin filaments) and myosin filaments (thick filaments) slide past one another to produce contraction (shortening) of muscle cells. In non-muscle cells, actin micro-filaments provide support and shape. They also assist in cell movement (in phagocytes and cells of developing embryos) and movements within cells (secretion, phagocytosis, pinocytosis).

Microtubules are larger than microfilaments. They are relatively straight, slender, cylindrical structures that consist of a protein called tubulin. The major centre for assembly of micro-tubules is an organizing region known as the centrosome. Together with micro-filaments, micro-tubules help support and shape cells. Micro-tubules also function like a conveyor belt to move various substances and organelles through the cytosol, and they assist in the movement of phagocyte pseudopodia.

Intermediate filaments, so-named because their size is in between that of micro-filaments and micro-tubules, are exceptionally strong and tough. Several proteins form intermediate filaments. They provide structural reinforcement inside cells, hold organelles (such as the nucleus) in place, and associate closely with micro-tubules to give shape to the cell.

ORGANELLES

Despite many chemical activities occurring at the same time in the cell, there is little interference of one reaction with another. This is because the cell has many different compartments provided by its organelles (little organs). These are specialized structures that have characteristic appearances and specific roles in growth, maintenance, repair, and control. The numbers and types of organelles vary in different kinds of cells, depending on their functions.

NUCLEUS:

The nucleus is usually a spherical or oval organelle and is the largest structure in the cell. Within the nucleus are most of the hereditary units of the cell,

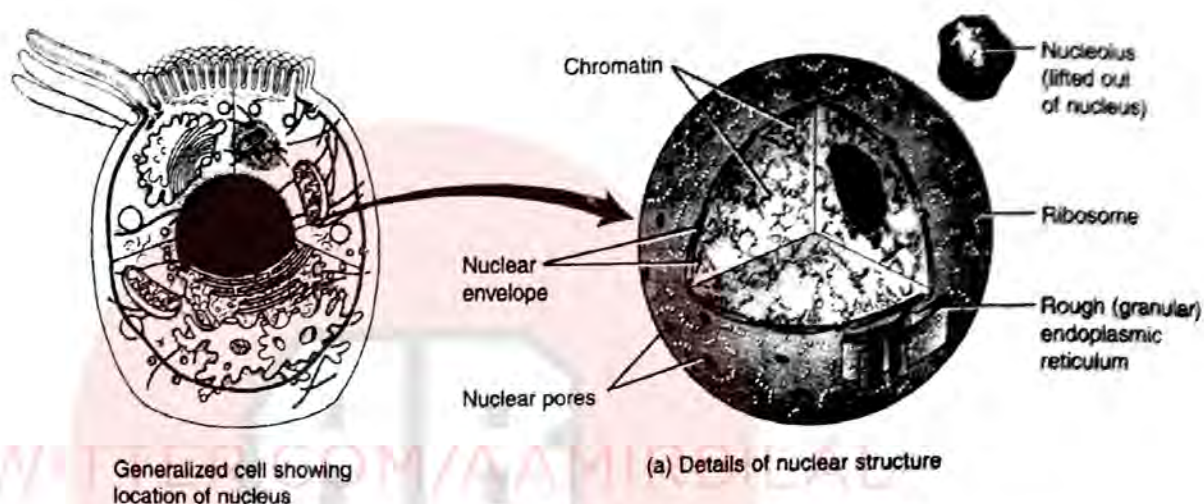


Fig. 1.19: The nucleus.

called genes, which control cellular structure and direct many cellular activities. The nuclear genes are arranged in single file along structures termed chromosomes. Human somatic (body) cells have 46 chromosomes, 23 inherited from each parent. Most body cells contain a nucleus, although some, such as mature red blood cells, do not. Skeletal muscle cells and a few other cells contain several nuclei.

FUNCTIONS OF THE NUCLEUS:

1. Controls cellular structure.
2. Directs cellular activities.

A double membrane called the nuclear envelope separates the nucleus from the cytoplasm. Both layers of the nuclear envelope are phospholipid bilayers similar to the plasma membrane. Water-filled nuclear pores in the envelope allow most ions and water-soluble molecules to shuttle between the nucleus and the cytoplasm. Because nuclear pores are about ten times larger in diameter than the pores of channels in the plasma membrane, even large molecules such as RNA and various proteins can pass through (fig. 1.19).

One or more spherical bodies called nucleoli are present inside the nucleus. They are clusters of protein, DNA, and RNA that are not enclosed by a membrane. Nucleoli are the sites of assembly of ribosomes and contain a type of RNA called ribosomal RNA (rRNA). Nucleoli disperse and disappear during cell division and reorganize once new cells are formed.

A chromosome is a very long DNA molecule that is coiled and packed into an amazingly compact structure together with several proteins. In a cell that is not dividing, the 46 chromosomes are a tangled mass of stringy threads, which is called chromatin and has a hazy appearance under the light microscope. Electron micrographs reveal that

chromatin has a "beads-on-a-string" structure. Each "bead" is a nucleosome and consists of double-stranded DNA wrapped twice around a core of eight proteins called histones. Histones help to organize the coiling and folding of DNA. The "string" between "beads" is linker DNA, which holds adjacent nucleosomes together. Another histone promotes coiling of nucleosomes into a larger diameter chromatin fibre, which then folds into large loops. In cells that are not dividing, this is the extent of DNA packing. However, before cell division the DNA replicates (duplicates) and the loops condense even more into chromatids. During this stage of cell division, a pair of chromatids constitutes a chromosome that is easily seen as a rod-shaped structure under the light microscope.

CENTROSOME AND CENTRIOLES:

Near the nucleus is a dense area of cytoplasmic material with radiating micro-tubules called a centrosome (fig. 1.20). Centrosomes serve as centres for organizing micro-tubules in nondividing cells and for forming the mitotic spindle during cell division. Within the centrosome is a pair of cylindrical structures called centrioles. Each centriole is composed of nine clusters of three micro-tubules arranged in a circular pattern. Centrioles lack the two central single micro-tubules found in flagella and cilia. The long axis of one centriole is at a right angle to the long axis of the other. Centrioles play a role in the formation and regeneration of flagella and cilia.

GENE ACTION:

Although cells synthesize many chemicals to maintain homeostasis, much of the cellular machinery promotes protein production. Cells are basically protein factories that constantly synthesize a large number of diverse proteins. The proteins, in turn, determine the physical and chemical

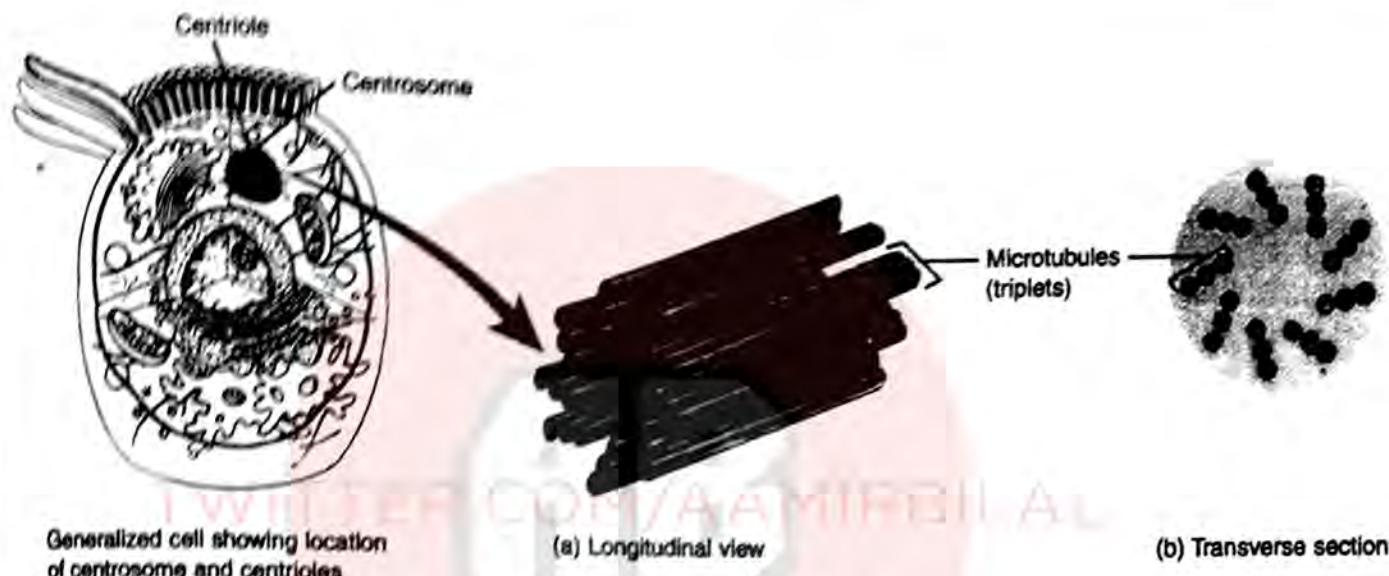


Fig. 1.20: Centrosome and Centrioles.

characteristics of cells and therefore of organs. Some structural proteins are helping in formation of plasma membranes, microfilaments, microtubules, centrioles, flagella, cilia, mitochondria, and other parts of cells. Other proteins serve as hormones, antibodies, and contractile elements in muscle tissue. Still other proteins are enzymes that regulate the rates of chemical reactions that occur in the cells.

The instructions for making proteins are contained in DNA. Cells make proteins by translating the genetic information encoded in DNA into specific proteins. In this process, the information in a region of DNA is first transcribed (copied) to produce a specific molecule of RNA. Then, the information contained in RNA is translated into a corresponding specific sequence of amino acids in a newly produced protein molecule. DNA directs protein synthesis by two principal steps in the production of proteins i.e. transcription and translation.

TRANSCRIPTION:

Transcription is the process by which the genetic information encoded in DNA is copied to a strand of RNA. The genetic information stored in the sequence of bases in DNA nucleotides serves as a blueprint or template for rewriting the same information into a complementary sequence of bases in RNA nucleotides. Three forms of RNA are made from the DNA template:

1. Messenger RNA

Messenger RNA (mRNA), that directs synthesis of a polypeptide chain.

2. Ribosomal RNA

Ribosomal RNA (rRNA), that comes together with ribosomal proteins to make up ribosome.

3. Transfer RNA (tRNA)

Transfer RNA (tRNA), that binds to amino acids during translation. Each tRNA can bind specifically to one of the 23 different types of amino acids. One can thus define a gene as a sequence of DNA that codes for a particular mRNA or rRNA. Because no two people have the same DNA molecules, unless they are identical twins, the nucleotide sequence is the key to each person's uniqueness.

Transcription of DNA is catalysed by the enzyme RNA polymerase. During transcription, bases pair in the same manner as they do in the DNA double helix. The base cytosine (C) in the DNA template dictates the base guanine (G) in the new RNA strand; the base "G" in the DNA template dictates the base "C" in the RNA strand; and a thymine (T) in the DNA template dictates an adenine (A) in the RNA. Since RNA contains uracil (U) instead of thymine, the base "A" in the DNA template dictates the base "U" in the RNA. As an example, if the template portion of DNA has the base sequence ATGCAT, the newly transcribed RNA strand would have the complementary base sequence UACGUA.

A	U
T	A
G	C
C	G
A	U
T	A
Template DNA base sequence	Complementary RNA base sequence

Only one of the two DNA strands serves as a template for RNA synthesis. This strand is referred to as the *sense strand*. The other strand, the one not

transcribed, is the complement of the sense strand and is called the *anti-sense* strand.

Within DNA are regions, called *introns* that do not code for synthesis of part of a protein. Introns are located between regions called *exons*, which are regions that do code for parts of proteins. Initially, a mRNA transcript includes both introns and exons. The RNA regions corresponding to DNA introns, however, are deleted (cut out) and the exons are spliced (rejoined) before mRNA leaves the nucleus and enters the cytoplasm to proceed to the next step of protein synthesis. This process, called mRNA splicing, deletes about three-fourths of the original RNA. A single gene may be able to code for more than one protein if the initial RNA transcript can be spliced in different ways to make different mRNAs. During cell differentiation, for example, some splicing patterns may change to produce different proteins at particular stages of differentiation. Once synthesized, mRNA, rRNA and tRNA leave the nucleus of the cell. In the cytoplasm, they participate in the next principal step in protein synthesis i.e. translation.

TRANSLATION:

Just as a DNA molecule provides the template for making a mRNA, so mRNA provides a template for synthesizing a protein. Translation is the process whereby the nucleotide sequence in a molecule of mRNA specifies the amino acid sequence for a protein molecule. In the mRNA molecule, each set of three consecutive nucleotide bases is called a codon and specifies one amino acid. Most mRNA molecules contain 300-3000 nucleotides. Since each set of three nucleotides codes for one amino acid, most proteins contain between 100 and 1000 amino acids. The term genetic code refers to the set of rules that relates the base sequence of DNA, the corresponding codons of mRNA, and the amino acids that the codons represent.

The key events of translation are as follows:

1. In the cytoplasm, the small ribosomal subunit binds to one end of the mRNA molecule and finds the *start codon*, a sequence where translation will begin. The large ribosomal subunit then joins in.
2. In the cytosol, each type of transfer RNA binds to one kind of amino acid and brings it to the ribosome. One end of the tRNA carries a specific amino acid, and another part of each tRNA has a triplet of nucleotides called an *anti-codon*.
3. By base pairing, the tRNA anticodon recognizes and attaches to a complementary codon on mRNA. For example, if the mRNA codon is AUG, then a tRNA having the *anti-codon* UAC would attach. In

the process, the tRNA brings along the specific amino acid, methionine in this case.

4. Once the first tRNA has attached to mRNA, the ribosome moves exactly three nucleotides along the mRNA, and the next tRNA, carrying its amino acid, moves into position.

5. When an amino acid attaches to its tRNA, ATP is used to form a high-energy bond between the amino acid and the tRNA. Such an activated amino acid can form a peptide bond with a second amino acid if the second amino acid is brought into correct position by its own tRNA. The larger ribosomal subunit contains the enzymes needed for peptide bond formation. As the peptide bond forms, tRNA detaches from the first amino acid.

6. The proper amino acids are brought into line, one by one, peptide bonds form between them, and the protein progressively lengthens. Each time the ribosome moves one codon along the mRNA, an "empty" tRNA is ejected. The released tRNA can then pick up another molecule of the same amino acid.

7. When the specified protein is complete, synthesis is terminated by a special *stop-codon*. The assembled protein is then released from the ribosome.

8. After protein synthesis, the large and small ribosomal subunits separate.

As each ribosome moves along a mRNA strand, it "reads" the information coded in mRNA and synthesizes a protein according to that information. Thus the ribosome synthesizes the protein by translating the nucleotide codon sequence into an amino acid sequence. Protein synthesis progresses at a rate of about 15 amino acids per second. As the ribosome moves along the mRNA and before it completes synthesis of the whole protein, another ribosome may attach behind it and begin translation of the same mRNA strand. In this way, several ribosomes may be attached to the same mRNA. This assembly is called a polyribosome. Several ribosome moving together along the same mRNA molecule permit the translation of one mRNA into several identical proteins almost simultaneously.

Remember that the base sequence of the gene determines the sequence of bases in mRNA, which in turn, determines the order of amino acids in a given protein. Thus each gene is responsible for making a particular protein as follows:



RECOMBINANT DNA:

Different kinds of cells make different proteins following instructions encoded in the DNA of their genes. Since 1973, scientists have been able to alter those instructions in bacteria, viruses, and yeast cells by inserting genes from other organisms. This causes the host organism to produce proteins it normally does not synthesize. Organisms so altered are called recombinants, and their DNA, a combination of DNA from different sources, is called recombinant DNA. When recombinant DNA functions properly, the host will synthesize the protein specified by the new gene it has acquired. The new technology that has arisen from manipulating the genetic material is called *genetic engineering*.

The practical applications of recombinant DNA technology are enormous. Strains of recombinant bacteria are now producing many important therapeutic substances. These include human growth hormone (hGH), required for growth during childhood and important in metabolism of adults; *insulin* a hormone that helps to regulate blood sugar level and is used by diabetics; *interferon* (IFN) an antiviral (and possibly anticancer) substance; *factor VIII* a blood clotting factor missing in people with haemophilia A; *erythropoietin*, a hormone that stimulates formation of red blood cells; *monoclonal antibodies* to diagnose and treat cancer and assist in AIDS research; and many other substance. Scientists are also using recombinant DNA techniques in attempts to develop vaccines against several viruses, including those that cause *AIDS*, *herpes*, and *influenza*.

NORMAL CELL DIVISION:

Most of the cell activities mentioned thus far, maintain the life of the cell on a day-to-day basis. However, somatic cells ultimately become damaged, diseased, or worn out. New cells must be produced by cell division as replacements. In a 24 hours period, the average adult loses billions of cells from different parts of the body. Cells that have a short life span, such as cells of the outer layer of skin, are completely replaced every few days. In addition, cell division produces new somatic cells for tissue growth and new germ cells, which are specialized to form sperm and egg cells.

Cell division is the process by which cells reproduce themselves. It consists of a nuclear division and a cytoplasmic division. Because nuclear division can be either one of two types, two kinds of cell division are recognized.

In the first kind of division, *somatic cell division*, a single starting cell called a parent cell divides to

produce two identical cells called daughter cells. This process consists of a nuclear division called mitosis and a cytoplasmic division called cytokinesis. The process ensures that each daughter cell has the same number and kind of chromosomes as the original parent cell. This kind of cell division replaces dead or injured cells and adds new ones for tissue growth.

The second type of cell division, *reproductive cell division*, is the mechanism by which sperm and egg cells are produced. These are the cells needed to form a new organism. The process consists of a special nuclear division called meiosis (reduction division) followed by cytokinesis.

MOLECULAR CLONING:

It is a strategy to insert a DNA fragment of interest e.g. *segment of human DNA*, into a DNA molecule called a vector; that is capable of independent replication in a host cell. The result is a recombinant molecule or molecular clone composed of "DNA-insert" linked to vector- DNA sequences. Large quantities of inserted DNA can be obtained if the recombinant molecule is allowed to replicate in an appropriate host.

ENDOPLASMIC RETICULUM:

The endoplasmic reticulum (ER) is a system of membrane-enclosed channels of varying shapes called cisterns or cisternae (Fig.1.21). The ER is continuous with the nuclear envelope. The two types of ER are rough (granular) ER, which is studded with ribosomes, and smooth (agranular) ER, which has no ribosomes.

FUNCTIONS OF ENDOPLASMIC RETICULUM (ER):

1. Provides surface area for chemical reactions.
2. Transports various molecules from one part of the cell to another.
3. Rough ER stores newly synthesized molecules and forms glyco-proteins.
4. Rough ER and Golgi complex synthesize and pack materials to be secreted by the cell.
5. Smooth ER is the site of synthesis of fatty acids, phospholipids, steroids and detoxification of various chemicals.
6. In muscle cells, sarcoplasmic reticulum (derived from ER) releases calcium ions, which initiates muscle contraction.

Ribosomes associated with rough ER synthesize proteins. The rough ER also serves as a temporary storage area for newly synthesized molecules and may add sugar groups to certain proteins, thus forming glyco-proteins. Together, the rough ER and

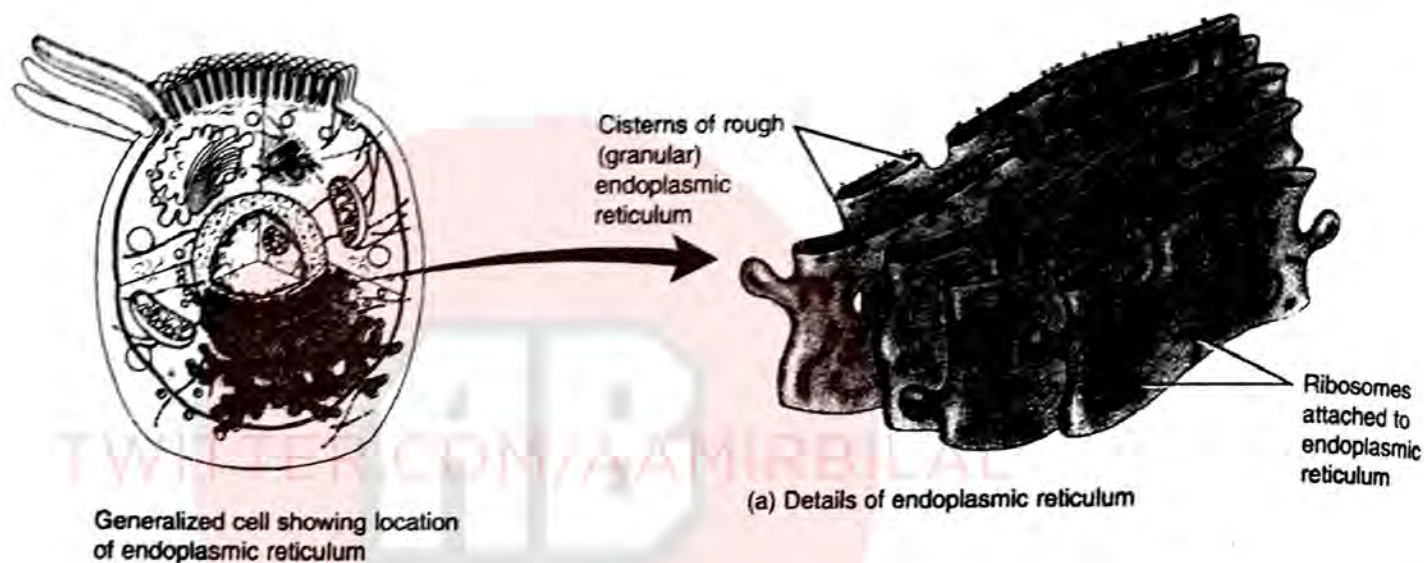


Fig. 1.21: Endoplasmic reticulum.

the Golgi complex synthesize package molecules that will be secreted from the cell.

Smooth ER is the site of fatty acid, phospholipid, and steroid synthesis. Also, in certain cells, enzymes within the smooth ER can inactivate or detoxify a variety of chemicals, including alcohol, pesticides, and carcinogens (cancer-causing agents). In muscle cells, calcium ions released from the sarcoplasmic reticulum, which resembles smooth ER, trigger contraction.

GOLGI COMPLEX:

The Golgi complex is an organelle located near the nucleus (fig.1.22). In cells with high secretory activity, the Golgi complex is extensive. It consists of flattened sacs called cisterns (cisternae), stacked upon each other like a pile of plates with expanded

bulges at their edges. Associated with the cisterns are small Golgi vesicles, which cluster along the expanded edges of the cisterns.

FUNCTIONS OF THE GOLGI COMPLEX:

1. Processes, sorts, and packs proteins and lipids for delivery to the plasma membrane.
2. Forms lysosomes and secretory vesicles.

The Golgi complex processes, sorts, packages, and delivers proteins and lipids to the plasma membrane and forms lysosomes and secretory vesicles. All proteins destined for export from the cell follow a similar route. Proteins and lipids destined for inclusion in the plasma membrane or for use inside lysosomes also pass through the Golgi complex.

A trip of proteins through a Golgi complex normally

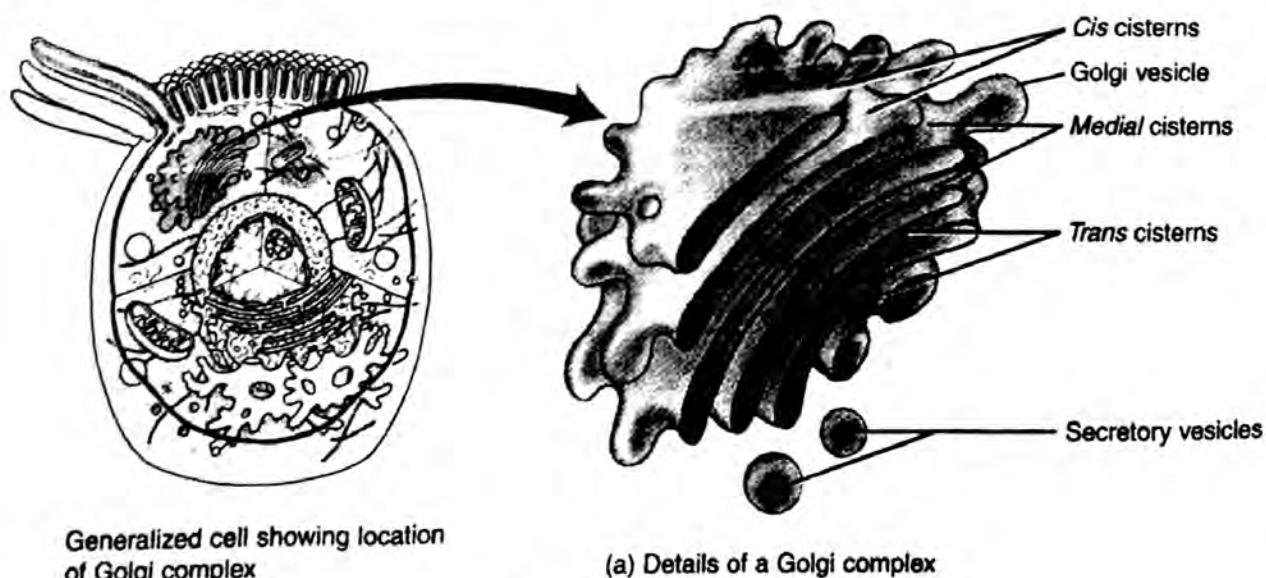


Fig. 1.22: Golgi complex.

occurs as follows.

1. From ribosomes the proteins move to rough ER, within the cistern of the rough ER, proteins (and glycoproteins) become surrounded by a piece of the ER membrane, which forms a transport vesicle.
2. The transport vesicle buds off the ER and moves to the Golgi complex.
3. Here, the vesicle fuses with the side of the Golgi stack closest to the ER, which is termed as cis or entry cistern. As a result of this fusion, the proteins enter the Golgi complex.
4. Once inside, they move through the cis cistern into a medial (middle) cistern. Their movement from one cistern to the next is probably by way of vesicles that bud from the edges of each cistern in the stack.
6. As the proteins pass through the Golgi cisterns, they are modified in various ways depending on their function and destination. After moving through one or more medial cisterns, the proteins enter the trans or exit cistern.
7. The trans cistern packages the modified proteins into vesicles.
8. Some vesicles become secretory vesicles, which undergo exocytosis to discharge their contents into the extra cellular fluid. Certain cells of the pancreas secrete digestive enzymes in this way. The vesicle membrane prevents the enzymes within from digesting the contents of the pancreatic cell itself.
9. Other vesicles that leave the Golgi complex are loaded with digestive enzymes intended for use within the cell. They become organelles called lysosomes.

CYSTIC FIBROSIS:

Sometimes a disorder results from faulty instructions for routing of a molecule. Such is apparently the case in cystic fibrosis, a deadly inherited disease that affects the air-ways, pancreas, salivary glands and sweat glands. The cause of cystic fibrosis is a genetic mutation affecting a transporter protein that carries chloride ions across the plasma membrane of many epithelial cells. The protein produced by the mutated cystic fibrosis gene fails to reach the plasma membrane, where it should be inserted to help pump chloride ions (Cl^-) out of certain cells. Evidently, the pump protein becomes stuck in the endoplasmic reticulum or Golgi complex and never reaches its correct destination. The result is an imbalance in the transport of fluid and ions across the plasma membrane and excessive build-up of mucus outside certain types of cells. The mucus clogs the lining of the airways to the lungs, causing breathing difficulty, and prevents proper secretion of digestive enzymes by the pancreas.

RIBOSOMES:

Ribosomes are tiny granules that contain ribosomal RNA (rRNA) and many ribosomal proteins. The rRNA is synthesized by DNA in the nucleolus. Ribosomes were so named because of their high content of ribonucleic acid. This particular type of RNA was subsequently named rRNA to distinguish it from the other types of RNA in the cell. Structurally, a ribosome consists of two sub-units, one about half the size of the other (fig.123). Functionally, ribosomes are the sites of protein synthesis.

FUNCTIONS OF RIBOSOMES:

1. Ribosomes are sites of protein synthesis.

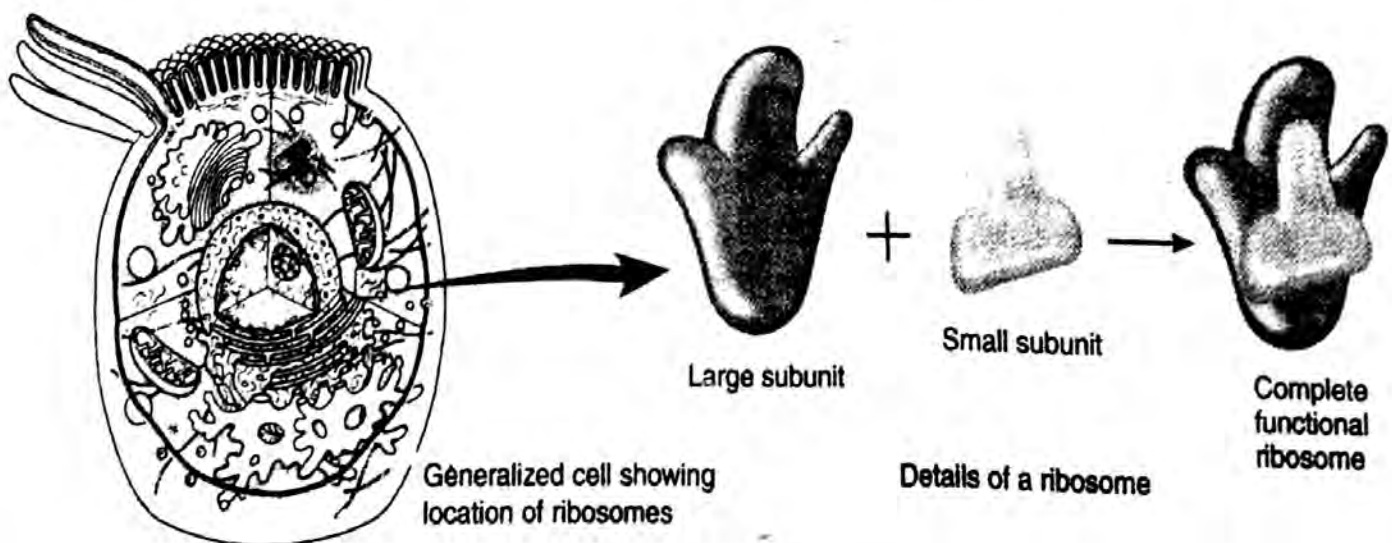


Fig. 1.23: Ribosomes.

2. Free ribosomes are involved with synthesis of proteins for use inside the cell.

3. Ribosomes attached to endoplasmic reticulum are involved with synthesis of proteins destined for insertion into the plasma membrane or export from the cell.

Some ribosomes, called free ribosomes, float in the cytosol; they have no attachments to other organelles. The free ribosomes occur singly or in clusters, and they are concerned primarily with synthesizing proteins for use inside the cell. Other ribosomes attach to a cellular structure called the endoplasmic reticulum. These ribosomes are involved in the synthesis of proteins destined for insertion in the plasma membrane or for export from the cell.

LYSOSOMES:

Lysosomes are membrane-enclosed vesicles that form in the Golgi complex. Lysosomes contain as many as 40 kinds of powerful digestive (hydrolytic) enzymes capable of breaking down a wide variety of molecules. Some disorders are caused by faulty lysosomes. For example, Tay-Sachs disease is an inherited absence of a single lysosomal enzyme. This enzyme normally breaks down a membrane glycolipid (called ganglioside GM_2) that is especially prevalent in nerve cells. As GM_2 accumulates, the nerve cells function less efficiently. The child becomes blind, demented, and uncoordinated and dies, usually before the age of 5.

Lysosomal enzymes work best at an acidic pH. The lysosomal membrane includes active transport pumps that drive hydrogen ions (H^+) into the lysosomes. Thus the interior of a lysosome has a pH of 5, which is 100 times more acidic than the cytosolic pH of 7.

Lysosomal enzymes digest bacteria and other substances that enter the cell in phagocytic vesicles

during phagocytosis, pinocytic vesicles during pinocytosis, or endosomes during receptor-mediated endocytosis. Eventually, the products of digestion are small enough to pass out of the lysosome into the cytosol. There, they are recycled to synthesize various molecules needed by the cell.

Lysosomal enzymes also help to recycle the cell's own structures. A lysosome can engulf another organelle, digest it, and return the digested components to the cytosol for reuse. In this way, organelles are continually replaced. The process by which worn-out organelles are digested is called autophagy. A human liver cell recycles about half its contents, a process known as autolysis. Autolysis occurs after death and in some pathological conditions. Lysosomes also function in extra-cellular digestion. Lysosomal enzymes released at sites of injury help to digest cellular debris, which prepares the injured area for effective repair.

PEROXISOMES:

Another group of organelles similar in structure to lysosomes, but smaller, are classed as peroxisomes. They are so named because they usually contain one or more enzymes that use molecular oxygen to oxidize (remove hydrogen atoms) various organic substances. Such reactions produce hydrogen peroxide (H_2O_2). One of the enzymes in peroxisomes, called catalase, uses the H_2O_2 generated by other enzymes to oxidize a variety of substances, including phenol, formic acid, formaldehyde, and alcohol. All of these are toxic substances that may enter the blood stream. This type of oxidation is especially important in liver and kidney cells, where peroxisomes detoxify many potentially harmful substances.

MITOCHONDRIA:

Known as the "power houses" of the cell, mitochondria are the main sites for generation of ATP. A mitochondrion consists of two membranes

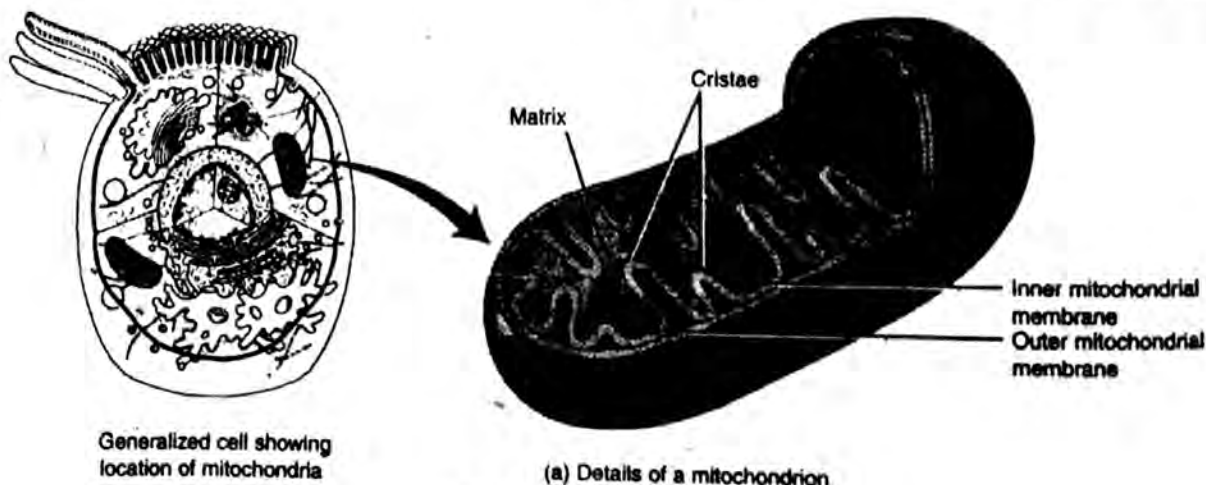


Fig. 1.24: Mitochondria.

each of which is similar in structure to the plasma membrane. The outer mitochondrial membrane is smooth, but the inner membrane is arranged in a series of folds called cristae. The central cavity of a mitochondrion, enclosed by the inner membrane and cristae, is called the matrix (fig. 1.24).

The elaborate folds of the cristae provide an enormous surface area for a series of chemical reactions known as cellular respiration, which provides most of a cell's ATP supply. Enzymes that catalyse these reactions are located in the matrix and on the cristae. Active cells, such as muscle, liver, and kidney tubular cells, have a large number of mitochondria and use ATP at a high rate.

Mitochondria self-replicate; they divide to increase in number. Their replication is controlled by genes within the mitochondria (mitochondrial DNA). Self-replication usually occurs in response to increased cellular need for ATP and at the time of cell division. Although each cell's nucleus contains genes from both mother and father, mitochondrial genes usually are inherited only from mother.

CELL INCLUSIONS:

Cell inclusions are a large and diverse group of chemical substances produced by the cells; some have recognizable shapes, but these are not bounded by membranes. These products are principally organic molecules and may appear or disappear at various times in the life of a cell. Examples include melanin, glycogen, and triglycerides. Melanin is a pigment stored in certain cells of the skin, hair, and eyes. It protects the body by screening out harmful ultraviolet rays from the sun. Glycogen is a polysaccharide that is stored in liver, skeletal muscle, and the inner lining of the uterus and vagina. When the body requires quick energy, liver cells can break down the glycogen into glucose and release it into the blood. Triglycerides, which are stored in adipocytes (fat cells), may get broken down to synthesize ATP.

CELL JUNCTIONS:

Most epithelial cells, some muscle cells, and some nerve cells are tightly joined to form a close functional unit. The points of contact between adjacent plasma membranes are called cell junctions. Three principal types of cell junctions serve distinct functions i.e.

1. Tight junctions form fluid-tight seals between cells like the seal on a ziploc sandwich bag.
2. Anchoring junctions fasten cells to one another or to the extra cellular material.
3. Gap junctions permit electrical or chemical signals to pass from cell to cell.

TIGHT JUNCTIONS:

Tight junctions are common among epithelial cells that line the stomach, intestines, and urinary bladder. They prevent fluid in a cavity from leaking into the body by passing between cells (fig. 1.25).

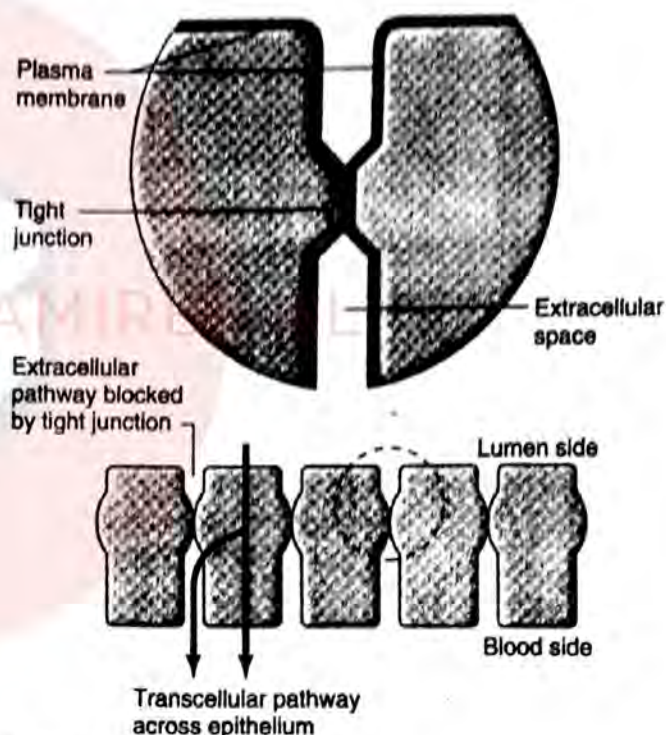


Fig. 1.25: Tight junction.

ANCHORING JUNCTIONS:

Anchoring junctions are common in tissues subjected to friction and stretching. Examples include the outer layer of the skin, the muscle tissue of the heart, the neck of the uterus (which is greatly stretched during childbirth), and the epithelial lining of the gastrointestinal tract. *The most common type of anchoring junction is called a desmosome.* These structures form firm attachments between cells some-what like spot welds. On the cytoplasmic surface of a desmosome, intermediate filaments of the cytoskeleton attach to a dense plaque of proteins (fig. 1.26).

GAP JUNCTIONS:

Gap junctions allow the rapid spread of action potentials from one cell to the next in some parts of the nervous system and in muscle of the heart and gastrointestinal tract. In a developing embryo, chemical and electrical signals that regulate growth and differentiation may travel by way of gap junctions. At a gap junction, adjacent plasma membranes approach each other, not fusing but leaving a gap of 2 – 3 nm (1 nm = 1/1,000,000,00 m), as shown in fig.1.27.

Spanning the gap are proteins called connexons that form minute fluid-filled tunnels. Through the connexons, ions and small molecules, such as glucose and amino acids, can pass directly from the cytosol of one cell into the cytosol of the next. Note that cancer cells do not have gap junctions and therefore cannot communicate with each other. As a result, cell division is not coordinated and occurs in an uncontrolled manner.

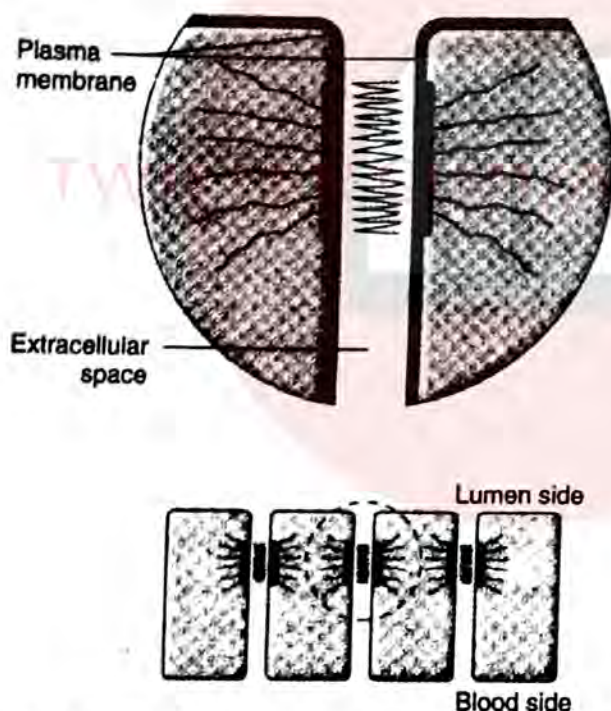


Fig. 1.26: Desmosome.

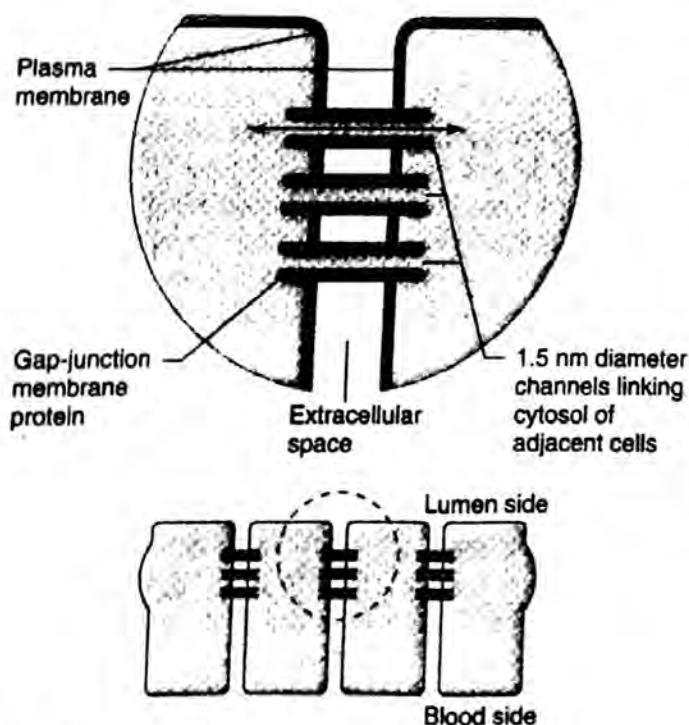


Fig. 1.27: Gap junction.

APPLIED CELL PHYSIOLOGY:

CANCER:

Cancer is second only to heart disease as a leading cause of death in the United States; approximately one-fourth of the population develop some form of cancer during their lifetimes, and a diagnosis of cancer is one of the most dreaded pronouncements a person can hear. The different forms of cancer differ greatly in mortality, either because they progress slowly, or because they are highly treatable.

When cell in some area of the body divides without control, the excess of tissue that develops is called a tumour, growth, or neoplasm. The study of tumours is called oncology, and a physician who specializes in this field is called an oncologist. Tumours may be cancerous and sometimes fatal, or they may be quite harmless. A cancerous growth is called a malignant tumour or malignancy. One property of a malignant tumour is its ability to undergo metastasis, the spread of cancerous cells to other parts of the body. A non-cancerous growth is called a benign tumour. Benign tumours do not metastasise, but they may be removed if they interfere with a normal body function or are disfiguring.

CAUSES OF CANCER:

What triggers a normal cell to lose control and become abnormal? Several factors contribute. First, there are environmental agents: substances in the air we breathe, the water we drink, and the food we eat. A chemical or other environmental agent that produces cancer is called a carcinogen. The World Health Organization estimates that carcinogens may be associated with 60 – 90% of all human cancers. Examples of carcinogens are hydrocarbons found in cigarette tar, radon gas from the earth, and ultraviolet (UV) radiation in sunlight. Adopting a cancer-prevention life-style and avoiding environmental carcinogens can help to decrease your risk of getting cancer.

Viruses are a second cause of cancer. These agents are tiny packages of nucleic acids, either DNA or RNA, that are capable of infecting cells and converting them to virus-producers. Although the link between viruses and cancer is strongly established for a variety of animal cancers, the relation in human cancers is less predictable. Clearly, the number of people infected with these viruses is much larger than the number who develop cancer. But evidence suggests that chronic viral infections are associated with up to one-fifth of all cancers.

CHARACTERISTICS OF CANCER CELLS:

The change from a normal cell to a cancerous cell is

called transformation.

1. TRANSFORMATION:

Cancerous cells lack the structural characteristics and functions of mature, differentiated cells. Cancerous cells of the lung, for example, cannot carry out normal lung functions. Transformed cells exhibit two heritable characteristics: anaplasia and autonomy.

a. ANAPLASIA:

Anaplasia is the lack of differentiation i.e. a lack of specialized form and function. Anaplastic cells resemble embryonic cells rather than mature cells. It is uncertain whether they result from mature cells reverting to embryonic form or from the multiplication of tissue stem cells that never differentiate in the first place.

b. AUTONOMY:

Autonomy refers to the fact that cancer cells are independent of the normal mechanisms that control the rate of cell division.

2. NUCLEAR ENLARGEMENT

Cancer cells typically show enlarged nuclei, abnormally dense DNA, and increased mitotic activity. Their rapid mitosis and lack of histological organization enable tumour cells to invade and destroy neighbouring tissues. This invasion is called progression.

3. METASTASIS:

In metastasis, loose cancer cells, travel in the blood or lymph, and invade distant organs, where they seed new tumours. Thus, lung and prostate cancers often metastasise to the brain, while colorectal, prostate, and breast cancers often metastasise to the lungs and liver.

4. ANGIOGENESIS:

Cancer cells also produce angiogenic factors, which cause many new blood vessels to grow into the cancer, thus supplying the nutrients required for cancer growth. Cancer cells continue to grow and proliferate at the expense of nutrition of the healthy cells. As a result, normal tissues gradually suffer nutritive death.

5. INTRACELLULAR AND SURFACE CHANGES:

- a. Reduction of modification of surface glyco-lipids and glyco-proteins.
- b. Loss of the glycoprotein fibronectin, resulting in changes in cell shape, cell-cell adhesion, cellular migration, and the location of receptors.
- c. Disruption of the cyto-skeleton, so that it is unable to maintain normal cell shape and cancer cell often becomes rounded

d. Changes in the nuclear envelope, including a decreased number of nuclear pores, development of projections and pockets, and blabbing, the formation of vesicular structures on the envelope.

e. Changes occur in chromosome structure or number. Structural changes can result when portions of a chromosome are broken off, deleted, or duplicated. Changes in chromosome number occur as entire chromosomes are gained or lost.

CANCER DETECTION AND DIAGNOSIS:

In a biopsy, a portion of the tumour is removed for microscopic examination. This enables the haematologist/oncologist to determine if the cells have any of the characteristics of cancer cells. Magnetic resonance imaging (MRI) or computerized tomography (CT), scanning can help to determine the size of the tumour, the extent to which it impinges on surrounding tissues and organs, and the extent to which it has metastasised.

SCAR TISSUE:

Scar tissue can cause adhesions, abnormal joining of tissues. They commonly form in the abdomen around a site of previous inflammation such as an inflamed appendix, or they can develop after surgery. Although adhesions do not always cause problems, they can decrease tissue flexibility, cause obstruction (such as in the intestine), and make a later operation more difficult. Surgery may be required to release adhesions.